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GUTHRIE McCONNELL, M. D.

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Pathology and Bacteriology for  
Dental Students

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# PATHOLOGY AND BACTERIOLOGY FOR DENTAL STUDENTS

BY

GUTHRIE McCONNELL, M. D.

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## PREFACE

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IMPORTANT as pathology and bacteriology are in the study of dentistry, there are certain facts that must be considered. Such students deal with a distinctly limited portion of the great extent of the above subjects, and consequently should not be expected to become specialists in them. Yet a thorough drilling in the underlying groundwork is essential. 21

It has become evident, therefore, as a result of several years of teaching, that the text-books as prepared for medical students contain much that can well be omitted from the dental curriculum. For that reason this manual has been prepared. One that is expected to contain a full presentation of general pathology and bacteriology and what additional along special lines as has been considered advisable. With a complete knowledge of the basic principles of these subjects, the student will then be able to apply them to his work, and later, if he so desires, to specialize. It is hoped that this volume will be found to accomplish the end desired.

GUTHRIE McCONNELL.

PHILADELPHIA, PA.

*February, 1915.*



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# PATHOLOGY AND BACTERIOLOGY FOR DENTAL STUDENTS

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## CHAPTER I

### PATHOLOGY

“**Pathology** is that subdivision of biology which has for its object the study of life in its abnormal relations.” It is the science that treats of disease in all its aspects.

By “disease” is meant any condition in which there is a variation from the normal aspect of the organism; it may be either a structural or a functional deviation.

Pathology also may be subdivided into two sections: one known as *morbid anatomy* and *histology*, in which the lesions are structural. The other, *morbid physiology*, in which the changes are functional.

The main heading may be again subdivided into *general pathology*, that deals with abnormal processes common to the entire organism, such as inflammation, fever, etc., and *special pathology*, that includes the changes within special organs.

Under **etiology** are considered the conditions giving rise to disease. They may be either *predisposing* or *exciting*.

Predisposing causes are those that in any way lower the vitality of the individual and thus render him more susceptible; such as bad hygienic surroundings, poor food, bad air, noxious gases, fatigue, extremes of temperature, drugs, injury, pre-existing disease.

Exciting causes include mechanical forces, sudden extremes of heat and cold, electricity, poisons, parasites, and also certain mechanical abnormalities, such as defects in the heart-valves.

Although the causes are divided into these two classes, a predisposing cause if acting with great severity may readily excite disease.

The individual may be the seat of two diseases, one acting primarily and another following secondarily.

The latter may be either the direct result of the primary or may have nothing whatever to do with it. Infection of the lung by the tubercle bacillus gives rise to phthisis; later on there may be involvement of pleura or of intestines, or a person suffering from chronic nephritis will often die from a secondary pneumonia.

**Traumatism** may cause disturbances of function more or less marked according to the extent, severity, rapidity, and duration of its action.

If it takes the form of constant pressure, there will be malnutrition and atrophy of the part on account of the interference with the blood-supply. If the pressure is intermittent, hyperemia may occur and hypertrophy take place.

When the force is sudden the lesions vary according to the instrument used. If sharp, there are lacerations; if dull, contusions.

According to the locality, there may be fractures and concussion. In all these injuries there is greater or less destruction of tissue, followed by the phenomena of inflammation, with either recovery or death.

**Temperature.**—Following the local action of extreme *heat* a condition known as a *burn* results, in which there is relaxation of the blood-vessels, exudation of serum, and possibly of blood. The extent of the injury to the tissues depends on the degree of heat and its time of action. According to the extent, burns may be divided into four classes: (1) Hyperemia of the exposed surface; (2) extravasation of serum and liquefaction of certain cells, thus forming vesicles; (3) coagulation of the cellular protoplasm with resulting necrosis and extension into the deeper tissues; (4) charring of the tissues and extensive, deep involvement.

Death may result from burns, either immediately from shock or later from exhaustion, from a perforating ulcer of

the duodenum, or from toxic substances formed either within the body or absorbed from the skin. There may be marked alterations within the blood and their action may prevent the kidneys from carrying on their functions.

The cause of the duodenal ulcer is not clear, but may depend upon thrombosis of some small vessel and subsequent digestion by the gastric juice. As a rule, a burn, even of the first degree, will prove fatal if it involves one-third the surface of the body.

If the exposure has been general, the result will vary according to the cause, whether steam, dry air, or sun, etc. Exposure to dry air or sun may cause heatstroke or heat exhaustion. In the first there occur symptoms of heart failure, dyspnea, and coma, if severe. Usually the pulse is full and rapid, face flushed, very high temperature, dry skin, labored breathing, unconsciousness, and muscular relaxation. In heat exhaustion the skin is moist, cool, pale, pulse small and soft, unconsciousness unusual, and temperature may be subnormal.

*Extreme cold* will bring about conditions very similar to those resulting from heat, and will have various symptoms, according to whether the effects have been superficial or deep. In the former the tissue may completely recover, but in the latter the blood-vessels may be involved and gangrene follow.

The primary effect of cold is to bring about a contraction of the superficial blood-vessels. This, however, gives way to a paralytic dilatation, on account of which more blood enters the chilled part and the entire body will be affected.

If the tissue should freeze during the stage of contraction, the part would appear pale; if during that of dilatation, it would be swollen and dusky in color.

**Electricity** causes destruction of tissue either by the heat generated or by the resistance of the body to its passage.

Death may result instantly from disturbance of the nervous system or there may be extensive and destructive burns. Sometimes there is involvement of internal organs.

**X-rays** when applied too closely or for too great a length of time occasionally give rise to a dermatitis or even to burns

of the first, second, or third degrees. As a sequel to the dermatitis, squamous-celled carcinoma has quite frequently developed and gone on to a fatal termination.

**Barometric pressure** may cause disturbances if it be either greatly increased, as in deep-sea divers or caisson-workers, or diminished, as in mountain-climbers and in persons ascending in balloons. In the latter the blood shows an increase in the number of red corpuscles, in their specific gravity, and in their hemoglobin content.

**Season** also has a distinct effect upon disease; pneumonia and bronchitis being most common in winter, typhoid fever and malaria in spring, yellow fever and enteric disorders in the summer. In cold weather certain diseases become more frequent on account of the crowding of the people.

**Intoxication.**—A *poison* is a substance which when introduced into the living body in a relatively small amount will disturb the structure or functional activity. These substances may be formed within the body through faulty metabolism and give rise to *endogenous* or auto-intoxication. They may result also from faulty elimination, irregular absorption, incomplete chemical transportation, or excessive glandular secretion. They may be introduced from without, *exogenous* intoxication. The exogenous may be (1) *immediate* and *indiscriminate* in their action or they may be (2) *remote* and *selective*.

1. The first group includes the *caustics* and *irritants*. Their effects are the more marked the greater the concentration, and may be purely local. The poison may, however, be absorbed and give rise to remote effects. In this class belong the salts of the heavy metals, a few vegetable substances, and some animal products.

The effects may vary from a slight reddening to marked necrosis and sloughing. They are brought about by abstracting the water from the tissue, by coagulating the albumins, and forming definite compounds with the elements. The effect depends on various conditions both of the individual and of the poison. If a patient has been addicted to the use of a drug, a dose fatal to others may cause in him very slight disturbance, a condition known as tolerance, and not similar

to immunity. Sometimes a very large dose may cause vomiting, and the poison is in that way removed.

2. Many of the first group come secondarily into this class by being absorbed and taken up into the blood. They may unite with the hemoglobin or they may bring about *hemolysis*, a destruction of the red corpuscles.

When the poison combines with the hemoglobin, forming methemoglobin, the union is so close that the oxygen can no longer be taken up and supplied to the tissue. Death then results from a general asphyxia. Instead of death, cyanosis may develop, this commonly resulting from the use of coal-tar products.

Strychnin is selective in its action, in that it stimulates the respiratory centers and the motor nerves. Bromids depress them.

**Foreign bodies** that are not living may cause disease by mechanically interfering with the functions of the body. The most important causes of disease are, however, *bacteria*, the lowest forms of vegetable life. They are almost ubiquitous and give rise to many disturbances of function. It is not, however, always possible to prove the relationship between bacteria and disease. Koch has advanced four laws. They are: (1) The bacteria must be found in the diseased individual; (2) they must be capable of cultivation upon media outside the body; (3) pure cultures introduced into a healthy animal must produce the disease in the animal; (4) the bacteria must be recovered from the inoculated animal.

Diseases caused by bacteria are capable of transmission from a person to person and are generally termed *infectious*. They may gain entrance into the body through abrasions of the skin and mucous membranes, through the air or by means of the digestive tract, through the genito-urinary tract, or they may be transferred from the maternal to the fetal blood in the uterus.

**Animal parasites** may frequently be the cause of disease. To this class belong the various intestinal worms and certain blood organisms, as the plasmodium of malaria, the filaria, the trypanosomes, etc.

## CHAPTER II

### DISORDERS OF METABOLISM

By **metabolism** is meant those physiologic processes brought about in living tissue by means of which the individual is able to form new tissue and reintegrate the old. Under this head comes the rejection of those substances that are unfit for use in the bodily economy.

In order that the functions of the body be carried on in a normal manner it is necessary that the amount taken up by the cells must balance the output. The metabolic equilibrium must be maintained. To carry on the work it is not sufficient that new material be taken in, more is required. These new substances must be assimilated by the body, broken down into various parts, and the waste portions excreted. Disturbances of any of these above factors, constituting metabolism, may give rise to diseased conditions of varying importance.

When the tissues are unable to carry on these molecular exchanges a pathologic condition exists. This may be either functional or structural, the latter generally being secondary to the former.

Metabolism may be divided into two classes, according to whether simple substances are built up into complex, or the complex broken down into the simple. The building-up or constructive variety is called *anabolic metabolism*; the breaking down or destructive, *catabolic metabolism*.

By means of catabolism the "end products," those substances not required by the body, are formed, such as urea, water, etc. Anabolism is concerned in the rearranging of molecules so as to render them suitable for food.

A food is a substance that will form new or reintegrate old tissues. It may be either in excess or in diminution, or may

vary in quality, the amount required depending upon the activity of the individual.

The assimilation of food depends upon the presence within the gastro-intestinal tract of certain digestive ferments, which may vary greatly in quantity.

The *protein* substances are acted upon by the pepsin in the stomach and the trypsin from the pancreas. Pepsin acts in an acid medium; trypsin, in an alkaline. The necessary acid in the stomach is the hydrochloric. Changes from the normal amount of pepsin are unusual, but there may be great variations as far as the acid is concerned. It may be increased, *hyperchlorhydria*; diminished, *hypochlorhydria*; or absent, *achlorhydria*. If absent or much diminished, the food, not being properly digested, will undergo fermentation. If there be any obstruction at the pylorus the stomach will tend to dilate.

The *carbohydrates* are acted upon first in the mouth by the salivary ferment, *ptyalin*; then in the intestines by *amyllopsin*, a ferment derived from the pancreas.

The *fats* are acted upon by *steapsin*, a pancreatic ferment, and by the bile.

The condition of the individual depends upon the assimilation of the food, which may be abnormal in quantity or quality.

If the quantity taken up by the individual is diminished, either by lack in amount or by being deflected from its proper channels, certain pathologic conditions will result. These may be *emaciation* or *starvation*, in which case the body weight diminishes, the temperature falls, and the energies all fail. At first the reserved food is called upon. The circulating proteins are first used up, then the glycogen, and afterward the fats and the muscles. The heart and the central nervous system are the last structures to be involved. The organs become smaller, the excretions and secretions are gradually suspended. In the blood the leukocytes become much fewer, although the red cells appear in normal number. This is probably due to the loss of the blood-serum. Death takes place slowly, either from exhaustion, disorders of metabolism, or by terminal infections.

In **marasmus**, a term applied to babies and old people, the wasting away takes place more slowly than in starvation. In it the trouble is very frequently not due to lack in quantity of food, but to improper assimilation.

If during the course of a definite disease these symptoms of slow starvation appear, the condition is called **cachexia**. In it there is a peculiar yellowish color of the skin and also a marked anemia. It is probably due to the formation of toxic substances, many resembling ferments, which produce injurious effects upon the normal tissues of the body.

**Rickets**, or **rachitis**, is a condition of childhood that is indicated by structural changes of the bones, particularly those of the pelvis and of the lower extremities. It is characterized by an excessive formation of cartilaginous bone followed by a deficient deposit of bony salts. Such bones are not perfectly rigid and tend to show more or less deformities on that account. Eventually enough salts may be deposited to render the bone rigid, but it will retain its irregular structure. In these children dentition is late and the teeth readily undergo carious changes.

If larger amounts of food are taken than are necessary for the bodily requirements, the excess will be carried through the intestines unacted upon. It may result in an excessive formation of fatty tissue, giving rise to the condition known as *obesity* or *polysarcia*. This is due either to the excessive absorption of food, either fats or substances, like carbohydrates, whose catabolism yields fats, or to inadequate combustion of the fats so acquired. In some cases both factors may play a part.

In **asphyxia** there is a lack in the amount of oxygen and an increase in the carbon dioxide. In this process there is first a period of increase in the inspiratory efforts, then in the expiratory, and finally exhaustion. After death the heart, particularly the right side, is found to be distended with blood.

**Dyspnea** is a slight lack of oxygen, sufficient to stimulate but not to depress the respiratory centers. *Cyanosis*, a bluish color of the skin, particularly of the face, then appearing. *Apnea* is a condition in which there is a period when no respiratory action takes place.

Abnormalities in the secretions of the organs may cause marked disturbance. The secretions may be either *internal* or *external*. The external pass directly from the glands by means of ducts. The internal pass slowly into the blood, which carries them to all parts of the body. In addition to the actions of the better known internal secretions are others, called *hormones*, whose functions appear to be to stimulate to full activity other digestive glands, even those situated at a distance.

The **thyroid secretion**, when lessened or absent, gives rise to the condition known as *myxedema*. In this the skin becomes much swollen and firm, particularly in the region of the face. The skin will not pit on pressure nor are the dependent portions affected. The hair frequently falls out, the voice undergoes changes, and there are commonly decided disturbances of mentality. If sheep's thyroid gland is given in such cases there is frequently a decided improvement.

**Cretinism** is a very similar but more severe condition resulting from disease of the thyroid during intra-uterine life or in early childhood, usually appearing during the first year. The child does not develop, remains a dwarf, there is more or less complete loss of mind, the lips are very thick, tongue large, and the abdomen very pendulous. Frequently several members of a family are found to be suffering from it. The state is also occasionally markedly hereditary.

If the thyroid secretion be increased, there may result *exophthalmic goiter*, or Basedow's disease. It is characterized by enlargement of the thyroid gland, paroxysms of palpitation of the heart, bulging of the eyes, and nervous excitement. In this the administration of sheep's thyroid increases the symptoms.

The relationship between the thyroid gland and general disease is not clearly understood. There appears to be distinct bearing upon the nervous system and also upon the metabolic processes taking place within the body. The active principle seems to be "thyroidin," a substance that contains nearly 10 per cent. of iodine.

The *parathyroids* are several small pea-like bodies situated

close to the thyroid, and histologically resemble the undeveloped thyroid. Their removal is followed by the condition called *tetany*, which manifests itself by exophthalmos, rapid respiration, and painful tonic muscular spasms, most marked in the hands and feet. These symptoms may be due to a loss of ability to neutralize toxins. Relief from them has been obtained by the intravascular use of a soluble lime salt.

The secretion of the **adrenals** is obtained from the medullary portion which is developed from the same source as the sympathetic ganglia. It is evidently derived from the chromaffin cells, so-called on account of their affinity for the chrome salts. Wherever those cells are present the active principle can be procured, the greatest collection being in the adrenal. This secretion is evidently of marked importance, as disease of or removal of those bodies causes severe disturbances in the individual. If completely removed, collapse and death occur within a few hours. When the breaking down has taken place slowly, a condition known as *Addison's disease* results. In it there is an increasing weakness, accompanied by anemia, emaciation, and a peculiar bronzing of the skin and mucous membrane of the mouth.

Whether or not it has a relation to the pigmentation of the skin and to the cachexia is not settled, but it is probably the result of oxidation by the secretion.

The action of the adrenal secretion seems to be more upon the vasomotor system. When applied locally the vessels will contract, and if injected into the circulation will cause a rise in blood-pressure. This is due to the contraction of the arterioles.

The secretion of the **pituitary body** seems to bear definitely upon the nutrition of the tissues. When diseased the condition of *acromegaly* is generally present. In it there is a marked enlargement of the bones of the face and of the extremities. The enlargement is due to an actual hypertrophy of the parts involved. Accompanying this there is usually some interference with speech, and the memory is slightly affected.

In the *pancreas*, besides the three external secretions, there is also an internal one. It seems to be chiefly concerned in carbohydrate metabolism; it is a glycolytic ferment.

**Diabetes** is a disease in which the carbohydrates are not properly assimilated, and is characterized by the persistent appearance of sugar, chiefly as dextrose, in the urine. In this way it differs from alimentary glycosuria, in which the sugar appears transitorily. The abnormal condition of the urine in diabetes is the direct result of an altered composition of the blood, which in turn is caused by changes in metabolism. Examination of the blood in diabetes always shows an increase of sugar above the normal of 0.1 per cent., a condition known as *hyperglycemia*. This increase of sugar may be due to any of the following conditions: (1) Impairment of the glycogenic function of the liver and muscles, caused by the cells being unable to store dextrose as glycogen; (2) impairment of the power of the muscles and other tissues to utilize dextrose; (3) overproduction of dextrose from glycogen, protein, or fat.

As the pathology of many cases of diabetes is so uncertain or obscure, it is difficult to classify them according to the pathologic conditions, but from the point of view of metabolism diabetic patients may be divided into two great groups: (1) Cases of mild diabetes, in which the glycosuria ceases as soon as the carbohydrates in their food have been sufficiently reduced. In most of these cases the glycosuria depends entirely upon the quantity or kind of carbohydrate in the food. (2) Cases of severe diabetes, in which the glycosuria does not cease as soon as their diet is freed from carbohydrates. They must, therefore, excrete dextrose derived from protein or fat as well as from carbohydrates.

**Mild Diabetes.**—This group may be divided into four varieties, according to the pathologic condition which causes the change in metabolism:

1. *Neurogenous diabetes* is caused by the action of the nervous system upon the liver. It has been shown that puncture at the tip of the calamus scriptorius in the fourth ventricle is followed generally by hyperglycemia and glycosuria. At present it would appear that this hyperglycemia following puncture is due to dextrose produced from hepatic glycogen, and that this conversion is an overproduction because it takes place irrespectively of the needs of the tissues. A similar condition may

occur in the course of tumors or diseases of the brain, as well as in fractures at the base of the skull.

2. *Hepatogenous Diabetes*.—In view of the importance of the glycogenic function of the liver in preventing hyperglycemia after carbohydrate meals, it is not surprising that parenchymatous disease of the liver may produce glycosuria.

3. *Lipogenous Diabetes*.—Patients suffering from any variety of mild diabetes may be fat, but there appear to be cases in which the diabetes has some direct connection, at any rate in point of time, with obesity. It has been suggested that there are patients who have lost the power of assimilating carbohydrates properly, but who do not have glycosuria as long as they retain the power of converting the excess of carbohydrates into fat. When this power becomes impaired, these patients develop glycosuria.

4. *Pancreatic Diabetes*.—In this variety there is a partial failure of the internal secretion of the pancreas which induces a mild degree of diabetes. Although this form of diabetes is pathologically distinct, clinically there is nothing to distinguish it from the other varieties considered. It has, however, been found that if the lesion progresses sufficiently the diabetes changes from the mild to the severe type, and of no other variety of mild diabetes does this hold true.

**Severe Diabetes**.—The essential feature in the metabolism of these cases is that they excrete dextrose derived not only from carbohydrate food, but also either from tissue fat or from protein food, or from both sources at the same time. This disturbed metabolism is evidently due to the absence of an internal secretion of the pancreas. Tying the pancreatic duct does not cause glycosuria, but extirpation of the organ gives rise to a glycosuria closely resembling diabetes and terminating fatally.

The structures most intimately concerned are the islands of Langerhans which are most numerous in the tail or splenic end of the gland, and are supposed to regulate the metabolism of sugar. If the lesions involve these structures, then diabetes ensues; if, however, the head end alone is affected, there may be no glycosuria. The common lesion of the islands is primarily

a connective-tissue overgrowth which frequently undergoes a degeneration belonging to the hyaline type. There is the formation of a homogeneous substance that stains with the acid dyes, but does not give the amyloid reaction.

The natural termination of all severe and progressive cases of diabetes is in coma due to the formation of acetone bodies, the mother substance of which is beta-oxybutyric acid. This on oxidation yields aceto-acetic acid, and this in turn, by the loss of  $\text{CO}_2$ , forms acetone. The main source of these acetone bodies is probably fat and not proteins, but it is quite possible that they do have a double source of origin, and that the relative quantities derived from the two sources will vary with circumstances.

According to the quantity and kind of acetone body excreted on a standard diet containing about 50 to 70 gm. of starch, it is possible to divide severe diabetes into three stages: In the first stage are those which secrete acetone alone, and in quantities which vary from the normal 0.05 to 0.5 gm. a day. Such cases retain considerable power of utilizing carbohydrates. The second stage is marked by the constant appearance of diacetic acid in the urine, and this always takes place when the excretion of acetone is more than about 0.5 gm. a day. Patients in this stage still retain some power of utilizing carbohydrates. The third stage begins when beta-oxybutyric acid is always present in the urine, and this is so when more than about 1 gm. of acetone is excreted in the day. Cases in this stage show little or no power of utilizing carbohydrates.

The coma that results is probably due to changes taking place within the cells of the body and not in the blood, the hypothesis at present being that the coma is due to a change in the reactivity of cells produced by the acidosis.

**Uremia** is a condition associated with disease of the kidneys and characterized by various clinical manifestations, as drowsiness, stupor, coma, twitchings of the muscles, cramps, convulsions, vomiting, blindness, and frequently death. The cause of this condition is not known. It evidently is not due to an increased amount of urea in the blood, as that substance has been proved to be but feebly toxic and incapable of producing

the symptoms of uremia. The evidence indicates the presence of poison, either singly or in a group. It may be due to the retention within the body of some substance that normally is excreted; to the abnormal decomposition in the blood or tissues of such a substance, or to the formation of abnormal products. Decomposition of urea may result in the production of ammonium carbamate and ammonium carbonate, and these substances when introduced into the circulation give rise to symptoms resembling those of uremia. Examination, however, of the blood in uremia does not show any excess of ammonia. It has been suggested that the kidney produces an internal secretion, and that uremia is due to some change in quantity or quality of this theoretic substance.

**Eclampsia** is a condition occurring in pregnant women that clinically seems closely allied to uremia, although it may be present without any albuminuria. When death takes place the liver will show congestion, capillary thrombosis, anemic and hemorrhagic necroses, and thrombosis. The kidney will present a nephritis ranging from a slight parenchymatous degeneration to an acute, intense nephritis. It is claimed by some that eclampsia is due to a deficient oxidizing capacity on the part of the liver which fails to convert protein derivatives into urea. There are others who believe that the toxic substances are probably derived from the fetus or the placenta.

**Gout, or podagra,** is a disease in which there is deposited within the joints, in the articular cartilages, uric acid and its compounds. It generally affects the small joints of the hands and feet, particularly the big toes. These salts may be deposited elsewhere, as tophi in the cartilages of the ear and in the meninges. As a result of these deposits the joints may be much deformed. Lesions of other portions of the body are usually present. There is a marked tendency toward the formation of connective tissue in the form of interstitial nephritis and of arteriosclerosis; fatty changes also take place in the heart and liver. Gout usually appears after middle life in those who have lived very well, drunk plenty of wine, and have not taken exercise. It is a chronic disease, but

exhibits periods of acute and painful inflammation lasting several days.

It is probably the outcome of insufficient oxidation, by which the precursors of uric acid and similar bodies are not fully oxidized, and by their accumulation and toxicity set up morbid changes.

The salts concerned are the sodium biurates and quadriurates, uric acid existing in the blood in the form of the latter. The soluble quadriurates circulating in the blood, if in the presence of uric acid and sodium salts in excess, are precipitated as insoluble crystalline biurates.

In **oxaluria** and **phosphaturia** there is an excess of either oxalic acid salts or of phosphates. The presence of oxalic acid is thought by some to be due to the amount present in the vegetable matter consumed, while others think it is the result of deficient oxidation of the carbohydrates. It is of chief importance in the formation of calculi, it being precipitated in the crystalline form mainly when there is an increased amount of calcium in the urine.

The phosphoric acid exists in the form of the phosphates of magnesium, ammonium, and sodium. These may form calculi in the bladder when they occur in excessive amount in an alkaline urine, as they remain in solution if the reaction is acid.

*Acetone* and *diacetic acid* are often found in the blood and urine in the later stages of diabetes.

The **bile** may vary in amount and consistency and may be prevented from passing into the bowel. The normal amount secreted varies from 500 to 1000 c.c. in a day. It is composed chiefly of water, but contains bile salts, cholesterin, lecithin, fat, and coloring substances. The salts are the glycocholate and the taurocholate of sodium. The important pigments are bilirubin and biliverdin, both of which are derived from the blood. Bilirubin undergoes oxidation to form various other pigments. It resembles hematoidin, and the toxic effects of the retention of bile seem to depend upon its presence, as when the bile is freed from its coloring-matters by filtration it is only one-third as toxic as in its original condition.

The most important function of bile is to increase the activity of the pancreatic ferments. It not only increases the fat-dissolving action of the steapsin, but it dissolves and increases the solubility of soaps, and so renders their absorption more easy. Consequently, if bile is absent from the intestines, but pancreatic juice is still secreted, from one-quarter to one-half of the fat taken in the food is unabsorbed.

Bile is not, as has been supposed, an antiseptic, consequently its absence from the intestinal contents neither increases the number of bacteria nor their fermentative or putrefactive activity.

If there should be any obstruction to the outflow of bile the condition known as **icterus** or **jaundice** follows. This obstruction may result from a catarrhal condition or a stenosis of the bile capillaries, inflammation of the common bile-duct, or of the papilla. It may be due to foreign substances, such as gall-stones, inspissated mucus, round-worms, or tumors within the large duct, or to pressure upon it from without. The jaundice is due to the absorption of the bile into the general circulation by means of the veins or lymphatics. A large amount of it is eliminated by the kidneys, while the excess is deposited within the connective tissues.

As a result of the absorption of the bile the skin is at first yellow, but if the condition continues for some time the pigment oxidizes and becomes greenish in color. This discoloration will be seen in the sclera, the lining of the arterial system, the mucous membranes, and in most secretions and exudations, normal or pathologic. The heart's action is frequently slowed (bradycardia) to 50 or even 20 beats a minute.

The effect upon digestion may be quite marked. There is found an excessive amount of fat in the feces. The stools become very light in color, due to the absence of hydrobilirubin, and may be very offensive on account of the loss of the laxative action of the hepatic secretion and consequent stagnation of the intestinal contents. There may be some interference with the outflow of the pancreatic enzyme, which would have a distinct effect upon the amount of fat present and also upon the color of the feces.

Sometimes there are marked nervous symptoms, probably the result of the presence of the biliary acids and salts in the circulation rather than due to the pigments.

Another form of jaundice is that of hematogenous origin. It occurs when no obstruction to the outflow of bile can be found. Although bile cannot be formed in any other place than in the liver cells, there are cases in which a general yellowish discoloration takes place without any hepatic lesion being present. It occurs in certain infectious diseases, as in yellow fever, malaria, etc., in poisoning by venom and tolulendiamin, and in the newborn in the form of icterus neonatorum. In all these conditions, particularly in the last named, there is a very marked destruction of the erythrocytes. The blood-pigment is changed into bile-pigment and thus stains the tissue. This form may be due to some nervous disturbances that cause a contraction of the circular muscles of the bile-ducts. It may be that there is an increase in the viscosity of the bile on account of the presence of the blood-pigments, and in that way the ready outflow is prevented. It has also been shown that the concentration of the bile is associated with an inflammatory condition of the bile-ducts.

Besides the secretion of bile the liver also forms urea and glycogen, but these two latter bodies are carried off in the blood.

**Intestinal disturbances** may bring about a condition of putrefaction accompanied by various symptoms of self-intoxication, inasmuch as the feces are made up of the remnants of digestion and of waste products. Their odor is due to the presence of indol and skatol.

The intestinal disturbances are due chiefly to the presence of bacteria and their products. Fermentation may take place in the stomach with the formation of acetic, lactici or butyric acids, or of alcohol. It results from the breaking down of the carbohydrates. In the intestine the proteins may undergo putrefaction and produce amido-acids, or aromatic bodies, as acetone, tyrosin, cresol, skatol, and indol. Ptomaines may be formed and give rise to many symptoms. These bodies resemble quite closely many of the vegetable

alkaloids and give rise to symptoms similar to those resulting from the drugs.

As a result of these disturbances *diarrhea* may occur. In this condition the feces are too soft and the bowel movements too numerous. It is an attempt to free the body of the irritating substances and may relieve the patient. The diarrhea may be due to increased rapidity of peristalsis, increased secretion of the intestines, diminished absorption by the large intestine, or disturbances of the controlling nervous mechanism, these depending upon many causes. These may be mechanical, inflammatory, infectious, obstructive, hepatic, and pancreatic.

*Constipation*, or *coprostasis*, is a condition in which defecation may not be sufficiently frequent, the amount of feces insufficient or abnormally dry and hard. It may be due to deficient motor activity of the colon as a result of weak muscle, deficient reflex activity, inhibition of the motor activity, uncontrolled and irregular motor activity. It may be due also to excessive force required to carry the feces to the pelvic colon. The work to be done by the intestinal musculature is excessive whenever the bulk or the consistence of the feces offers more than a normal degree of resistance, and whenever there is any narrowing of the intestinal lumen.

## CHAPTER III

### CIRCULATORY DISORDERS

THE circulation of the blood is maintained chiefly by two forces—the rhythmic contraction of the heart muscle and the elasticity of the arteries. Other factors concerned are the compression of the veins by the muscles and the inspiratory action of the chest.

As these are the chief factors, any abnormality within them will bring about more or less general disturbances of the circulation. To these may be added alteration in the quantity or quality of the blood itself. According as to whether the effect is more marked in the systemic or in the pulmonary circulations the disturbances are more or less widely distributed.

The circulatory disorders may be *cardiac* in origin and either the result of *muscular* or *valvular* lesions. If muscular, there may be an *excessive* or, what is more common, a *diminished* action.

The *excessive* form is seldom lasting, but while present causes a rise of blood-pressure, an increased amount of blood within the vessels in the part involved, and an increase in the rate of flow. If the overaction should be long continued, as a result of hard work or by constant stimulation, there would be hypertrophy of the left ventricle.

*Diminished* activity is more common and more important than the above. It may be brought about in many ways. It may be the sequel of a heart muscle weakened by the infectious fevers or other diseases, by poisons, by lack of nourishment caused by anemia, or by a blocking of the coronary arteries. It may be the result of nervous disturbances with no apparent lesion of the muscle, or it may be the result of some valvular disorder.

Sometimes it results from pressure from the outside—that exerted by collections of fluid in the pericardium, in the pleuræ, or by tumors or adhesions.

As a result of the weakened circulation there is an accumulation of blood in the venous circulation. If the failure is of the left ventricle, there will be a damming back of the blood in the left auricle and in the pulmonary circulation. If the right heart remains capable, the engorgement will go no further, but when it fails the right auricle becomes distended and a condition of general passive congestion ensues.

In all cases there is a decrease of arterial and an increase of venous pressure.

When the heart's action has become much weakened it will be found that the blood tends to gravitate to the more dependent portions, giving rise to *hypostatic congestion*. It occurs in the late stages of severe fevers and when death has taken place very slowly. The dependent tissues will become livid through the accumulation of blood, edematous from the escape of fluid from the blood-vessels, and sometimes bed-sores may result. A frequent occurrence is a collection of blood within the lungs, a condition known as hypostatic pneumonia.

The changes within the *arteries* may be either *organic* or *nervous* (vasomotor). Their elasticity may be diminished, and their caliber increased or diminished. The alteration in caliber may be due to changes within the tissues or to disturbances of the vasomotor control.

If there is a paralysis of the controlling nerves, the vessels dilate and hyperemia results. On the other hand, stimulation will cause contraction and subsequent anemia. When sufficiently marked, there will be an increase in the blood-pressure, interference with the heart's action, and venous congestion.

The most common *organic* disturbance is a sclerosis of the vessel wall, a condition leading to constant interference with the arterial circulation. Generally a hypertrophy of the left heart follows. If, however, the sclerotic changes are very widely distributed, instead of hypertrophy there may be a dilatation, on account of the resistance being too great for the heart to overcome.

Changes in the *quantity* of the blood, either an increase or a

decrease, are generally only temporary, and soon readjust themselves, either through a contraction or a dilatation of the vessels.

Alterations in the *quality* have a marked effect upon the circulation, probably through the direct action of the toxic substances upon the vessel walls or upon the terminal nerve filaments.

**Hyperemia.**—*General Hyperemia.*—There may be an increase throughout the body of the total volume of blood. This seldom remains for any length of time, as the various excretory structures of the body get rid of it. The condition known as plethora is the result of persistent overeating and drinking. It is usually associated with a hypertrophy of the left ventricle.

*Local hyperemia* is an increase in the amount of blood in a part of the body. It may depend upon either an increased supply to the part or be due to a diminished outflow—in one case a dilatation of the arteries, in the other an obstruction of the veins. The first is known as *active* or *arterial*, the second, as *passive* or *venous*, hyperemia.

*Active hyperemia* is an excess of arterial blood in a part. It occurs with increased functional activity (increased metabolism). It may be brought about through the central nervous system or by direct stimulation of the peripheral nerves. Any pathologic condition that will bring about a local dilatation of the arteries will cause active hyperemia.

The spinal cord or a nerve may be pressed upon as the result of a tumor or of an injury, and a paralytic dilatation occurs. The same condition follows the use of certain drugs acting peripherally either upon the muscular coat of the artery or upon the local nervous mechanism, or both.

In active hyperemia the part affected is redder than normal and more or less swollen as the result of the increased amount of arterial blood that it contains. The temperature is higher than in the surrounding parts, but never higher than that of the internal organs. There is also an increase in the rate of the blood-flow.

This form of hyperemia if continued for some time is followed by (1) hypertrophy of the part on account of the in-

creased nutrition, (2) parenchymatous degeneration from over-nutrition or overstimulation of the cells, and (3) a proliferation of the connective tissue around the blood-vessels.

It is found as one of the phenomena of inflammation. Post-mortem, it cannot be recognized on account of the contraction of the arterial walls, which drives out the blood. It may persist in the kidneys.

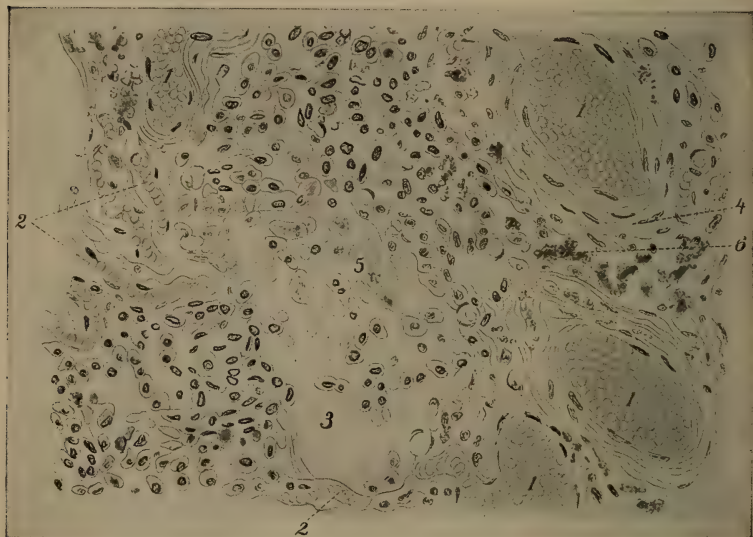


FIG. 1.—PASSIVE HYPEREMIA OF THE LUNG.  $\times 250$  (Dürck).

1, Ectatic and distended blood-vessels, filled with blood; 2, engorged and tortuous capillaries; 3, lumen of alveolus; 4, increased interlobular connective tissue; 5, cells, containing blood-pigment, within the alveolar lumen; 6, free, amorphous blood-pigment.

*Passive hyperemia* is an excess of venous blood in a part. It is the result of a distention of a vein on account of some obstruction to the outflow of the blood. This can be caused by obstruction within the veins or capillaries, as by thickening of their walls, by thrombi, or by pressure from without, as from a tumor. A common cause for general passive hyperemia is a lesion of the heart-valves. The circulation will

continue slowly unless the venous pressure becomes as great as the arterial, when it will stop, a condition known as *stasis*.

A part the seat of passive hyperemia becomes cyanotic, swollen, edematous, cooler than normal, and its function less. The rate of blood-flow is lessened. The edema is due to the escape of fluid from the blood. If severe, red corpuscles may escape.

Following long-continued passive hyperemia the tissues will undergo a fatty degeneration on account of the decreased nutrition, or even necrosis and gangrene may result. There may also be some increase in the amount of connective tissue. Pigmentation from escaped hemoglobin is not uncommon—*brown atrophy*.

When *stasis* occurs the blood-corpuscles slowly collect in the smaller vessels, the plasma is exuded, and the cells become packed closely together. Finally, the outline of the cells cannot be seen and the vessels appear to be filled with coagulated blood. Such is not the case, as when the circulation is re-established the corpuscles separate and move along as usual.

*Local anemia* or *ischemia* is the condition in which the part contains less than its normal amount of blood. It is most commonly due to obstruction by pressure of the flow of arterial blood into a part. This may be due to tight bandaging, pressure from a tumor, or to thrombi or emboli, or to changes in the wall of the vessel.

Disturbances of the vasomotor system may bring about marked lesions. If there is a good collateral circulation the area to which the obstructed vessel goes may show very slight change. If such is not the case, infarction may follow. An anemic area is pale in color, temperature lower, and functional activity decreased.

**Hemorrhage** is the escape of all the constituents of the blood through the walls of the heart or of the blood-vessels. It is divided into three classes, according to the vessel from which it escapes, as *arterial*, *venous*, or *capillary*.

It may occur by *rhesis*, in which case there is a demonstrable defect of the vessel wall, or by *diapedesis*, when there is

no discoverable lesion. The latter form occurs only from veins and capillaries. The method of escape of the corpuscles is not clear, but is generally supposed to take place through the stigmata of the lining endothelium. Hemorrhage by rhexis may be *primary* or immediate and *secondary* or recurrent; the first following immediately upon laceration of the vessel wall, the second occurring some time after the original injury.

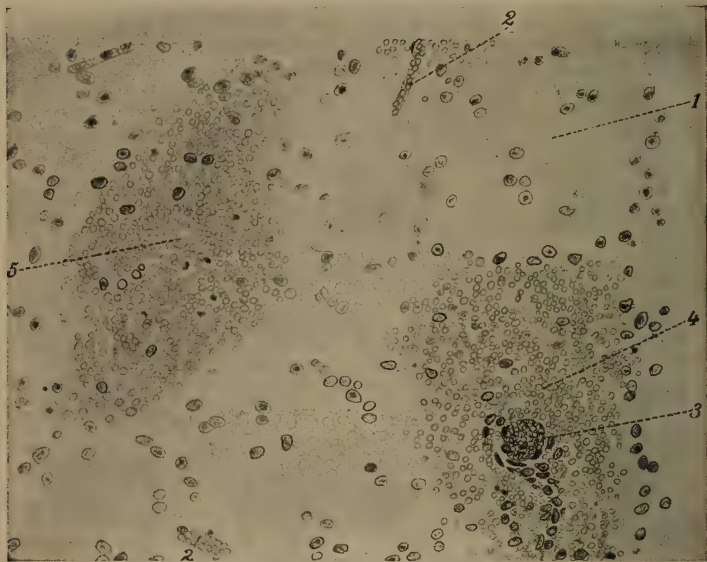


FIG. 2.—MULTIPLE CAPILLARY HEMORRHAGES IN THE CEREBRUM.  $\times 270$  (Dürck).

1, Cerebral substance; 2, engorged capillaries; 3, small artery with hemorrhagic infiltration of its walls; 4, hemorrhage by diapedesis in the tissues around a small artery; 5, smaller hemorrhagic foci without any connection with any blood-vessel visible in the section.

Hemorrhages may also be designated by special terms according to the area involved. *Petechiæ* are minute, circumscribed hemorrhages. *Ecchymoses* are of moderate extent; are what are commonly known as bruises. *Extravasations*, *suffusions*, and *sugillations* are conditions in which extensive areas are implicated. A *hematoma* is a collection of blood within a

solid tissue. A *hemorrhagic infarct* is a circumscribed hemorrhage within tissues, the result of the obstruction of an end-artery.

A hemorrhage may also have a special name according to its locality. *Cerebral apoplexy* is a hemorrhage brought about by a rupture of one of the arteries of the brain. According to the cavity in which it collects there may be a *hemothorax*, *hemopericardium*, etc. According to its method of escape from the body it may be known as *epistaxis*, bleeding from the nose; *hemoptysis*, from the lungs; *hematuria*, from the urinary tract, etc.

*Hemophilia*.—In it no structural changes in the vessel walls can be demonstrated, but severe bleeding takes place as the result of very slight injuries. In such individuals the hemorrhage resulting from the extraction of a tooth may be very dangerous and at times fatal. This condition is generally hereditary and is transmitted by the mother; as a rule the male children manifest the disease, but do not transmit it. On the other hand, the females pass it on to the males, but do not themselves manifest the disease. The most important change, and perhaps the only constant one, to be found in the blood in hemophilia is its lessened coagulability. This may be due to an excessive development of antithrombin, that substance in the blood which prevents coagulation within the vessels under normal conditions. It may be, however, that there is a lack of thrombokinase, the substance which brings about the coagulation of the blood under abnormal conditions. In some bleeders the amount of calcium present in the blood is decreased. Hemorrhage in such individuals has been successfully treated by the injection of normal blood-serum from man or horse. This probably supplies the necessary amount of thrombokinase.

*Hemorrhage by rhexis* may be caused by: (1) *Increased blood-pressure*, particularly in those cases in which, the blood-vessel walls being diseased, their elasticity is diminished. (2) *Disease of the vessels*, in which the walls become so weak that they are unable to withstand the normal pressure. (3) *Traumatism*, injury of some form sufficient to cause a lesion of the vessel wall.

*Hemorrhage by diapedesis* may follow in the course of (1) certain *diathetic* diseases, as scurvy, purpura hæmorrhagica, leukemia, hemophilia, etc.; (2) in severe *inflammations*; (2) in severe *hyperemia*, either active or passive; (4) in certain forms of *poisoning*, particularly that by snake-bite; (5) *alterations of innervation*; (6) in *hemophilia*.

*Spontaneous arrest* of hemorrhage takes place in several ways, but depends upon several factors—the direction of the injury, whether transverse or parallel to the axis of the vessel; the size and nature of the vessel, artery, vein, or capillary; the force of the heart's action and the blood-pressure, and the amount of fibrin-forming substances present in the blood: (1) When a vessel is injured its walls contract and the lumen is diminished in size. The vessel also, being elastic, retracts within the surrounding tissues. (2) The blood, coming in contact with abnormal surroundings, coagulates just outside, then upon, and finally within the vessel; this latter being known as a *thrombus*. In this way the vessel becomes plugged and the bleeding ceases. Another factor is that, as a result of the escape of large amounts of blood, the heart becomes weaker, even to a point where syncope may result; following this the blood-pressure falls and is unable to displace the clot.

The *results* of hemorrhage vary not only according to the amount of blood lost, but also as to the rapidity; if occurring slowly, the blood-forming tissues have time to supply the loss. Then, too, the results depend upon the locality of the hemorrhage, an ounce or so may prove fatal in cerebral apoplexy. If the amount has been small, there will be no ill effects; if comparatively large, weakness and unconsciousness; if very large, death will result from cerebral anemia. When the blood collects within the tissue various changes take place. It undergoes coagulation, a condition in which fibrin factors acted upon by fibrin ferments, in the presence of calcium salts, form a solid body known as fibrin. The greater the amount of fibrin, the more difficult is it for the tissue to recover. The fluid elements are first taken up by absorption by the lymphatics. The corpuscular elements and the fibrin break up, hemoglobin is set free, and the particles are scattered through the tissue. The greater part will be slowly

removed by the phagocytes, but some will remain. If the coagulation has been extensive the tissues may undergo a liquefaction necrosis, giving rise to a cyst.

**Thrombosis** is the coagulation of the blood within the vessels during life. It may depend upon changes within the blood, changes in the cardiovascular structures, and diminution of the velocity of the blood-flow.

The changes of the blood are those which tend to increase its coagulability. In the formation of a thrombus there is an action of the fibrin ferment or *thrombin* upon certain of the proteins in the blood-plasma. This ferment is not present in the normal circulating blood, but is produced after the blood is discharged from the vessels by the action of *thrombokinase* upon the *thrombogen* of the plasma in the presence of calcium salts. The thrombokinase is supposed to be liberated by the breaking down of leukocytes and blood-platelets. Certain chemical and physical substances—alcohol, ether, chloroform, heterologous blood-serum—when in the circulation may liberate fibrin ferments and thus cause thrombosis. The toxins of pneumonia, of diphtheria, and those resulting from extensive burns are especially active.

The lesions of the vessel walls are particularly important. Fibrin will be deposited upon the wall of the heart or blood-vessels whenever the nutrition of the endothelium of that wall is impaired. Diseases leading to the roughening of the endothelium, particularly arteriosclerosis, are important causes. Inflammation of neighboring structures may bring about changes within the intima. Ligation of a vessel causes an injury to the internal coat, and in that way predisposes to coagulation.

Diminution of the blood-flow may result not only from cardiac disturbances, but also from conditions causing a decrease in the lumen of the vessel. As the current slows, the leukocytes tend to adhere to the wall of the vessel, blood-plates make their appearance, and fibrin is deposited. The nutrition of the endothelium suffers, changes take place in the wall, and another factor in thrombosis then arises. The appearance of a thrombus depends upon the number of red

corpuscles contained within it, and that rests upon the varying rapidity of the blood-current at the time of formation. It is generally made up of superimposed layers of fibrin. After a thrombus has formed there is always a tendency for it to extend up the vessel, against the current of the blood, and to involve successive branches.

If the blood were passing through the vessel with *considerable velocity*, the thrombus would be grayish-white in color, and on section would show well-marked lamination. This is called a *white thrombus*.

If the blood were moving less rapidly, varying numbers of red cells would be entangled in the fibrin and the color would be brown or grayish red, giving rise to a *mixed* thrombus.

If it is formed in a short time from blood that is barely moving, a *red* thrombus will result.

A true thrombus differs from a postmortem clot within a vessel in that the latter is moister, is never adherent to the vessel wall, and never laminated. The clot may show also a division into pale, "chicken fat," and dark "currant jelly" portions as a result of the coagulation taking place after the heavier red corpuscles have sunk.

Thrombi may be classified according to their *etiology* as:

1. *Infectious*—those depending upon the entrance of bacteria into the circulation.

2. *Mechanical*—foreign bodies free from organisms.

According to their period of *formation* as:

1. *Primary* or *initial* thrombi.

2. *Secondary* or *consequential*, depending upon a pre-existing thrombus and usually extending to the first collateral branch of the blood-vessel.

According to their *morphology* as:

1. *Central*, *occluding*, or *obstructing*—formed by the coagulation of the entire mass of blood contained within a certain portion of the vessel.

2. *Parietal*—when attached to the wall of the vessel, but not completely obstructing it.

3. *Valvular*—parietal thrombi that have become partially detached.

4. *Channeled* or *tunneled*—those in which there still exists a lumen through which the blood can pass. May be the result of secondary changes in old thrombi.

5. *Ball*—thrombi that lie free within the cavities of the heart, usually in the auricles.

6. *Polypoid*—ball thrombi with pedicles.

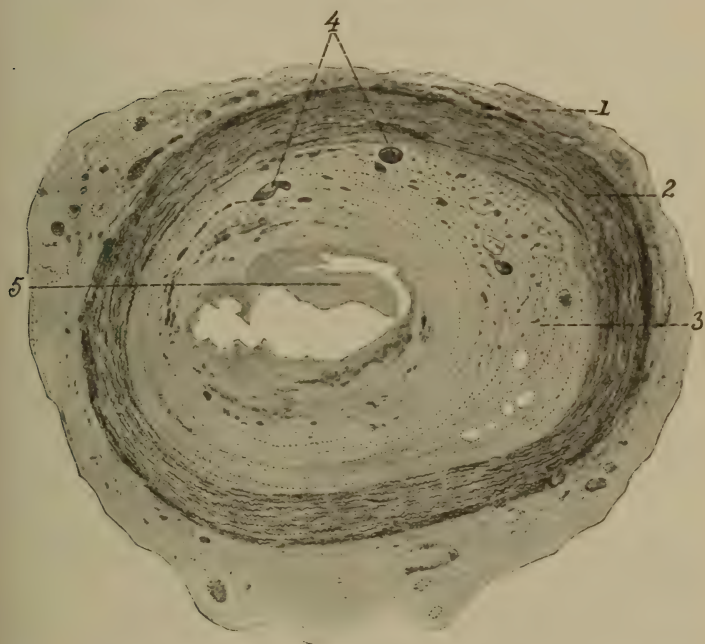


FIG. 3.—ORGANIZED AND PARTLY CANALIZED THROMBUS OF THE BRACHIAL ARTERY.  $\times 32$  (Dürck).

1, Adventitia; 2, tunica media; 3, organized thrombus—*i. e.*, replaced by connective tissue; 4, newly formed and in part dilated vessels within the thrombus; 5, disintegrated remains of the old thrombus.

*Metamorphoses of Thrombi.*—The ultimate fate of thrombi depends upon whether they are septic or aseptic. If septic, they must undergo disintegration. If aseptic, they may undergo *organization*—a condition that is not a transformation into, but is a replacement by, connective tissue.

They may undergo a central *liquefaction* or *softening*. The interior is broken down, blood-pigment set free, and leukocytes in varying numbers are present.

*Calcification*, particularly of small thrombi, giving rise to either *arterioliths* or *phleboliths*, according to whether they occur in arteries or in veins.

The connective tissue that replaces the thrombi will gradually undergo contraction until only a hard fibrous mass remains, the original lesion becoming converted into a scar.

The new tissue is derived from the endothelium of the blood-vessel and the fixed connective-tissue cells. As it forms, the thrombus undergoes absorption and breaks down into a mass, the granules of which are removed by the leukocytes.

If the thrombi contain living organisms they will be carried through the circulation and give rise to metastatic abscesses in various parts of the body.

The broken-down portions may become lodged in small vessels, and, acting as emboli, give rise to the condition known as embolism.

**Embolism** is the obstruction, complete or incomplete, of a blood-vessel due to the lodgment of a foreign body within that vessel, the circulating body being known as an *embolus*.

The most common variety of embolus is a dislodged portion of a thrombus, particularly those that occur upon the valves of the heart. Other emboli may be formed by cells of malignant tumors, masses of bacteria, blood parasites, particles of fat, pigment, air, etc.

The most common locality for emboli is within branches of the pulmonary artery, with immediate death or respiratory embarrassment resulting. The condition is most serious when vessels supplying important organs, as the brain, spleen, kidney, etc., are obstructed.

The *varieties* of emboli are: (1) *Simple, mechanical, or aseptic*; (2) *specific, infectious, or septic*.

The latter is the more severe, as in it suppurative conditions are associated with the mechanical.

*Retrograde* embolism occurs when, as in whooping-cough, the intrathoracic pressure is increased. An embolus in the

inferior vena cava may be carried in a direction opposite to the blood-current and be thus conveyed into the liver through the hepatic vein.

*Crossed* or *paradoxic* embolism occurs when the foramen ovale remains patulous. In this condition an embolus may pass directly from the venous to the general circulation without going through the pulmonary vessels.

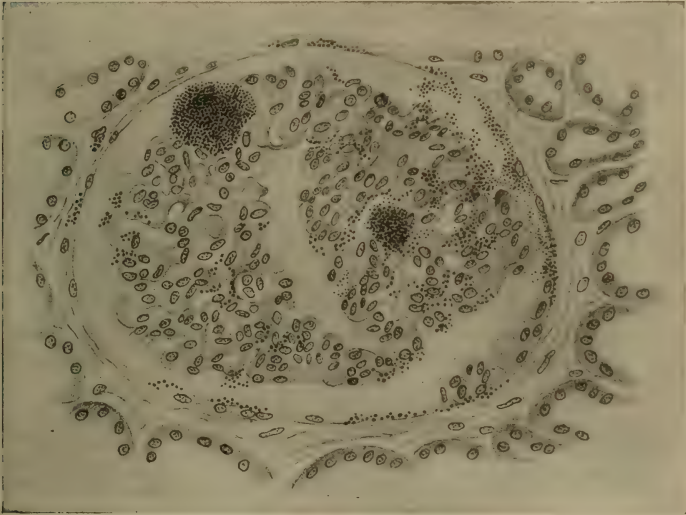


FIG. 4.—INFECTIOUS EMBOLISM OF THE KIDNEY FOLLOWING ENDOCARDITIS AND SHOWING GROUPS OF STAPHYLOCOCCI IN A GLOMERULUS (Dürk).

The results of embolism are numerous:

1. *Thrombosis* is a consequence of the stoppage of the flow of blood by the foreign body. The resulting thrombus may be much more extensive than the primary embolus.

2. *Inflammation* of the vessel walls is usually the result of the lodgment of the embolus, particularly if it is of the infectious type.

3. *Atrophy* may follow if the blood-supply is not quite

enough for the normal demands, but is yet sufficient to prevent actual death of the tissues.

4. *Necrosis* when the nutrition of a comparatively small area is cut off. Occurs chiefly in the internal organs.

5. *Gangrene* may result if the main artery of a part has been obstructed and the collateral circulation has been insufficient or unable to supply the demands.

6. *Aneurysmal* dilatation, especially in the brain, sometimes results.

7. *Infarction*.

**Infarction.**—An *infarct* is the area of degeneration and inflammation produced by embolism in an end-artery or where there is an absence of adequate anastomosis. The act of ob-

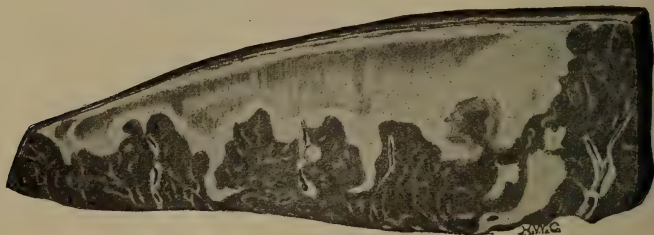


FIG. 5.—PART OF SPLEEN THE SEAT OF MULTIPLE ANEMIC INFARCTS (Coplin).

struction constitutes infarction, and must be sufficiently sudden to prevent the establishment of any collateral circulation.

Infarcts occur chiefly in the so-called end-arteries of Cohnheim—those that terminate in veins or capillaries without anastomosis with an artery. They are found particularly in the kidney, spleen, base of the brain and lungs, and sometimes in the heart.

The *varieties* of infarcts are: (1) *Anemic* or *white*; (2) *hemorrhagic* or *red*.

The *anemic* occur more commonly in solid organs, such as the kidney; the *hemorrhagic*, in organs whose structure is loose, as the lungs. The spleen may be the seat of either form.

An *anemic* infarct is one in which there is an absence of blood. The essential cause of this form is probably the rela-

tively rapid death of the tissues with coagulation before the capillary anastomoses have widened sufficiently to cause hemorrhage. There is usually a narrow hemorrhagic zone surrounding the lesion.

In this type there is probably present a secondary blood-supply sufficient to prevent the occurrence of coagulation necrosis.

A *hemorrhagic* one is where the obstructed area is full of blood. It may be the result of a back flow of blood from the veins (Cohnheim's theory) or from free capillary anastomosis. The latter would be particularly apt to occur when the local or general blood-pressure was previously elevated; or when the lodgment of an embolus caused a reflex contraction of the surrounding vessels and thus brought about an overflow of blood into the occluded area through the capillary anastomoses. Another theory is that the blood does not escape until there has been some degeneration of the vessel walls.

When the blood is cut off a conical shaped area of tissue is deprived of nutrition. As a result, necrosis soon starts in. The apex of this area is directed toward the interior of the organ, the base to the external surface. The base will be swollen and project above the surface of the surrounding tissues.

The infarct is, as a rule, firmer than the rest of the organ, except when it occurs in the central nervous system, where it is usually softer; the firmness depending upon the amount of coagulable material present.

Infarctions of the lung are unusual, as in that organ the capillaries are comparatively large, and the anastomosis between the pulmonary and bronchial arteries may be sufficient to prevent necrosis. To have infarcts occur within the lung, that organ must have been the seat of previous disease.

*Results.*—Infarction is always accompanied by necrosis and fatty degeneration. (1) The tissue may be restored by absorption and by collateral circulation. (2) It may be replaced by connective tissue with the formation of a scar. (3) It may become encapsulated. (4) Very rarely an infarct may undergo liquefaction necrosis with cyst formation, particularly in the brain.

**Edema**, or **dropsy**, is an excess of a clear watery fluid within the tissues between the cells. This fluid differs from the blood-plasma in that it has less albumin, is of a lower specific gravity, is rich in salts, but does not coagulate spontaneously, as it contains very little fibrin. This is called a *transudate* to distinguish it from the fluid present in inflammations, the latter being called an *exudate*.

It may be caused by:

1. Differences of pressure, a filtration process.
2. An increased secretion by the endothelial cells of the vessels.

3. Osmosis, resulting from variations in the relative concentration of salts, particularly sodium chlorid, on either side of the osmotic membranes, the cell walls.

4. The most satisfactory explanation of the occurrence of edema can probably be based upon the properties of colloidal (non-crystalloid) bodies such as gelatin and, presumably, other proteins. If dried gelatin is placed in water it will absorb a definite quantity of that water and will swell up to a certain point. If the water be slightly acidified the amount absorbed becomes very much greater. It has been shown that an inadequate supply of oxygen results in the production in the tissues of acids, particularly lactic acid and carbon dioxid, which, in turn, increase the tendency of colloids to take up water; consequently, edema is brought about. There is probably little of it due to increased capillary pressure or to secretory activity on the part of the endothelium of the blood-vessels.

5. **Neuropathic edema**, as herpes zoster and angioneurotic edema, may be due to something more than simple uncomplicated vasomotor disturbances.

6. **Hydrops**, or **edema ex vacuo**, is that which occurs when an organ, as a result of atrophy, does not completely fill its cavity, the remaining space becoming filled with fluid. It usually occurs in the cranial cavity and in the spinal canal.

The *types of edema* are as follows:

1. **Congestive edema**, the commonest form. Present in cases of obstruction to the venous outflow. Possibly the interference

with the nutrition of the tissues and the changes thus resulting play a part.

2. **Edema from lymphatic obstruction** does not occur in healthy tissues, but does take place if there is some disturbance of nutrition in the areas involved in the lymphatic obstruction.

3. **Inflammatory Edema.**—Probably due to degenerative changes occurring in the endothelial cells of the capillaries and of the tissue cells as well.

4. **Toxic Edema.**—Various toxic substances circulating in the blood have possibly different effects on the capillary walls.

According to the *seat* of the edema, special terms are employed.

When the subcutaneous tissues are generally involved, it is known as *anasarca*. *Ascites* refers to a collection of fluid within the abdominal cavity.

*Hydrothorax*, a collection within the pleural cavities.

*Hydropericardium*, when within the pericardium.

*Hydrocephalus*, fluid within the ventricles of the brain.

*Hydrocele*, when within the tunica vaginalis testis.

The common clinical causes are: (1) Cardiac insufficiency, the edema usually first noticed about the ankles. (2) Kidney disease, first seen about the eyes. (3) Cirrhosis of the liver, accompanied by ascites. (4) Anemia and cachexia. (5) Pressure upon the veins or lymphatics.

Under the microscope the cells of the involved tissues will appear more or less widely separated and in some instances may be vacuolated.

**Interstitial emphysema** is an infiltration of the tissues by gas, usually the result of some injury involving the respiratory tract. It may be due to the presence of some gas-producing bacteria, such as the bacillus of malignant edema or the *Bacillus aërogenes capsulatus*, within various organs, particularly the uterus and liver. It is a comparatively rare condition.

## CHAPTER IV

### RETROGRESSIVE PROCESSES

*Aplasia* signifies a total failure of development of a part.

*Hypoplasia* is an incomplete development.

### ATROPHY

**Atrophy** refers to a decrease in the size and in the functional activity of a part. It may be *general* or *local*.

In *general* atrophy the entire body wastes, a condition known as emaciation. It may be the result of lack of food, of starvation, or of disturbances of trophic influences with disorders of metabolism.

In *local* atrophy certain portions undergo changes which may be either *simple*, *degenerative*, or *numerical*, as the latter is sometimes called.

In the simple variety the individual cells undergo a decrease in size.

In the degenerative the number of cells is reduced as a result of disease. This is not considered a condition of true atrophy.

Atrophy may be brought about by there being no longer a demand made upon the part. Through lack of use the cells become smaller.

*Old age* is often accompanied by atrophy; is seen particularly in the sexual organs and in the loss of the elastic tissue of the skin.

*Pressure* is one of the commonest causes; occurs as a result of tight lacing, etc.

*Interference with the blood-supply* on account of the part not being supplied with a proper amount of nutrition.

*Disturbances of the trophic functions*, as in poliomyelitis.

The atrophied part will be smaller than normal, and frequently very irregular, causing elevations and depressions. Microscopically, the cells will be reduced in size, more or less degenerated, and frequently pigmented. The latter condition occurs commonly in the heart and is known as *brown atrophy*.

### DEGENERATIONS

Degenerations of cells can be divided into two forms:

1. *Infiltrations*, in which abnormal substances are deposited within the cells.

2. *Metamorphoses*, in which the protoplasm of the cell is transformed into abnormal substances.

"It was thought, but now seems less certain, that we could distinguish two processes which might accompany each other: one, the change wrought in the cytoplasm itself, leading to the appearance in the cell of such changed products; the other characterized by the appearance in the cytoplasm of substances obtained from outside the cell, and, it may be, imperfectly handled by the cell. It was thought that the former were degenerations proper and the latter infiltrations, but further study shows that it is becoming increasingly difficult to separate the two; that, in fact, they are too closely related to permit of being considered apart. Especially does it seem to be that true infiltration by itself is a rare occurrence. 'Infiltrated' materials, as fat, glycogen, etc., probably are the result of synthetic processes."

The changes in the cell may also be either *quantitative*, as when a normal substance is present in an abnormal amount; or *qualitative*, when there is an abnormal substance present.

*Necrobiosis* refers to the molecular or cellular death of a part.

**Parenchymatous Degeneration or Cloudy Swelling.**—In it the protoplasm of the cells contains an increased amount of protein substances. It accompanies very slight disturbances of nutrition, such as occur in inflammation; is found in all infectious diseases and intoxications, possibly as a result of increased bodily temperature, most likely as a result of disturbances of metabolism.

Although all the cells of the body, both glandular and stroma,

may undergo this change, they are not equally affected, the glandular ones being more liable to injury. The secreting cells have as their function the removal of certain substances from the body. If the blood contains injurious materials, these cells naturally will be the first affected, as they are the more intimately concerned.

This degeneration may follow extensive superficial burns, probably as a result of the action of the poisonous substances absorbed.

Microscopically the individual cells will be swollen and larger, more granular, and more opaque than normal on account of the presence of minute granules; the nucleus, consequently, may be obscured. These latter are insoluble in alcohol and ether, but are dissolved by alkalies and weak acetic acid.

The function of the cell is more or less disturbed, but complete recovery frequently occurs. If, however, the cause persists, fatty metamorphosis results.

**Fatty infiltration** is the deposit of fat within the cell or inter-cellular tissues. In all parts of the body, except the liver, the connective tissue is affected. In this organ the secreting or parenchymatous cells are involved. May be *general* or *local*. It may occur in cells that normally contain no fat, or else appear in excess in cells that do contain it.

The fat contained within the cells is made up of neutral palmitin, olein, and stearin.

Fatty infiltration may be *hereditary*, as obesity in successive generations; may result from *excessive nutrition*, particularly if combined with *lack of exercise*.

The use of *alcohol*, especially in the form of malt liquors. The alcohol, being easily oxidized, probably takes the place of the fats which remain unused.

*Anemia*, on account of the insufficient oxygenation of the tissues.

In certain *cachectic* conditions, as in phthisis; where the liver is frequently filled with fat.

The most common seats are the subcutaneous and subserous tissues, the omentum and the mesentery, in the liver, heart, kidney, and between the muscle-fibers.

Certain other regions, such as the subcutaneous tissue of the penis, nose, ear, lips, and eyelids, are never involved.

An organ the seat of fatty infiltration is larger, paler, mottled, streaked or diffusely yellow, softer, more friable, and greasy on section.

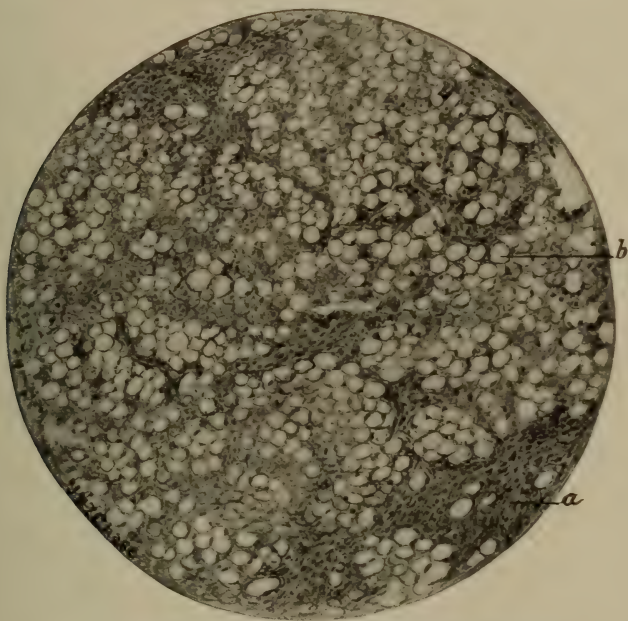


FIG. 6.—FATTY INFILTRATION OF THE LIVER (McFarland).  
*a*, Periportal connective tissue; *b*, fat drops in liver cells.

Under the microscope the fat may be found either inside or outside of the cells. If outside, it is most marked along the fibrous bands.

Inside the cell, particularly the glandular variety, the fat occurs in droplets which tend to enlarge and coalesce. The nucleus is displaced, giving the "signet-ring" appearance, or obscured; is seldom destroyed. The cell wall remains intact.

The *tests* for fat are sudan III, which stains it scarlet, or

a 1 per cent. solution of osmic acid, which stains black. It is soluble in alcohol, ether, and xylol; insoluble in water, acids, and alkalies.

*Adipocere* refers to the transformation of the fats into a wax-like substance most common in bodies that have been buried in damp earth.

**Fatty metamorphosis** is a conversion of the cell protoplasm into fat.

Generally speaking, the causes of cloudy swelling will bring about fatty degeneration if they are severe enough or act for a sufficiently long time. It occurs in *senility*, particularly when associated with marked arteriosclerosis and atheroma; in *anemia*, either as a result of hemorrhage or in diseases such as leukemia and pernicious anemia. The condition is probably more widespread in the latter than in any other disease. Occurs also in long-continued and high fever.

The most important substances causing the metamorphosis are the *poisons*, as the metallic salts, chloroform, coal-tar products, etc., and those formed by micro-organismal activity, as in yellow fever.

The fat present in the cells is either (1) formed by actual disintegration of the protoplasm of the cells, or (2) is taken up by the cells from the blood and remains unaltered, owing to defects in the vital power of the cell to assimilate it.

This condition may result from—

1. Insufficiency of the supply of nutriment.

(a) The blood-supply may be actually diminished.

(b) There may be increased work without a corresponding increase in the blood-supply.

(c) Actual deficiencies in the blood may impair its nutritive value, as diminution in the hemoglobin or of the corpuscles.

2. The failure of the cell to make use of the material placed at its disposal is probably the more important cause.

(a) The result of bacterial toxins.

(b) The influence of inorganic poisons.

(c) A senile change dependent upon the exhaustion of the inherited vital capacities of the cells.

Organs undergoing this change are generally smaller and

paler, yellowish, soft and flabby, and easily friable; they may undergo caseation.

The liver in yellow fever is a typical example.

Microscopically the cell protoplasm contains a large number of minute droplets that rarely coalesce. The nucleus is soon involved and ultimately is destroyed. The entire cell may break down into a fatty granular mass, sometimes called a "compound granule cell." Granules may be so small that their character cannot be recognized except by special staining.

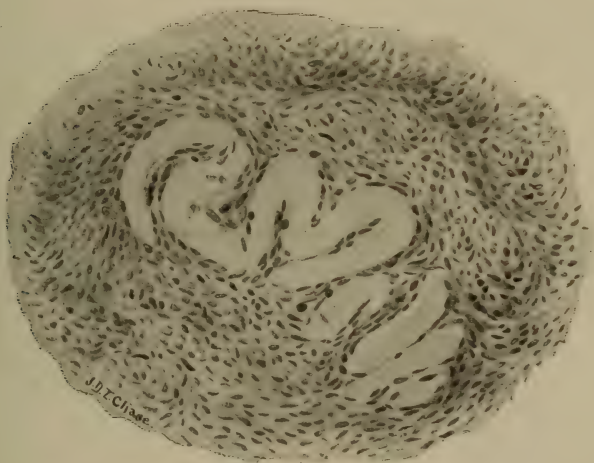


FIG. 7.—HYALINE DEGENERATION OF AN OVARIAN CAPILLARY. Oc. 2; ob. 9 (McFarland).

To distinguish between fatty metamorphosis and fatty infiltration is frequently not only difficult, but impossible, especially so in the liver. The droplets may coalesce in metamorphosis and remain separate in infiltration.

Crystals of margarín and the notched rhombic plates of cholesterin are frequently found in the fatty areas.

**Hyaline metamorphosis** is a conversion of cells and inter-cellular substance into hyaline material.

The cells of the connective tissue are most frequently involved, but epithelial and muscle cells may be affected.

The hyaline material occurs in the form of granules, is glistening and waxy, and with Van Gieson's method stains intensely red. Has no specific action with iodine.

It is at times scarcely distinguishable from amyloid metamorphosis.

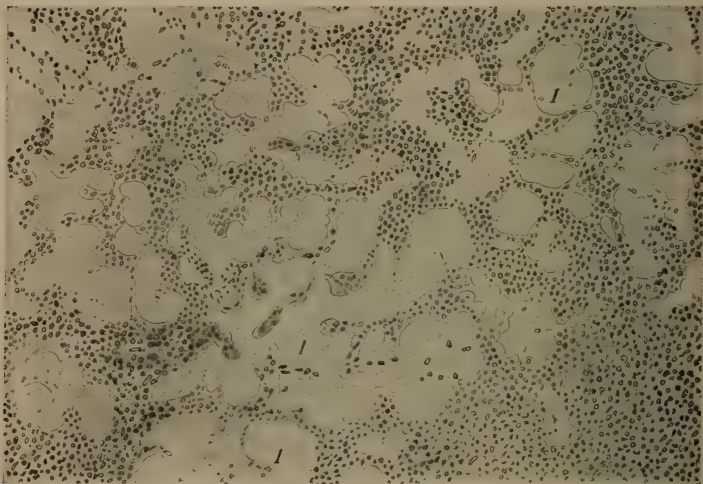


FIG. 8.—HYALINE DEGENERATION OF THE RETICULUM OF A LYMPH-GLAND IN TUBERCULOSIS.  $\times 280$  (Dürck).

Among the lymphocytes are seen single reticular fibers, which are greatly thickened and transformed into shining, homogeneous, non-nucleated bars (1).

It is found as a result of infectious diseases, septic processes, in chronic intoxications, such as lead-poisoning, and in new growths. Its formation is probably dependent upon some malnutrition of the tissues. Generally this form of degeneration is not sufficiently extensive to be recognized by the naked eye.

The most common site is in the endothelial and subendothelial tissues of the blood-vessels. The lumen will be narrowed or obliterated according to the extent of the thickening of the wall.

It also frequently occurs in the interstitial tissues, as between the renal tubules, between muscle-fibers, hepatic cells, and in the reticulum of lymph-nodes (Recklinghausen's degeneration). A third site is within the cells, particularly those of mesodermic origin.

It is either formed within the cell or, being formed elsewhere, has been brought to and deposited within the cell.

**Mucoid or myxomatous metamorphosis** is the conversion of cells and intercellular substances into mucin.

Mucin is insoluble in water, but will absorb it; is soluble in alkaline solutions, but is precipitated by weak acetic acid. When boiled with acids, will reduce Fehling's solution.

Either epithelial cells or the intercellular substances may undergo mucoid change. The latter is the more truly a metamorphosis.

It occurs in epithelial cells in all forms of catarrhal inflammation, in the cells of epithelial cysts, and in some carcinomata.

It is found in the interstitial tissues in both epithelial and connective-tissue growths, in some inflammatory conditions, and in myxedema.

The mucous membranes will be covered by a coat of thick, stringy, and viscid exudate. The underlying tissues may or may not show congestion.

Connective tissues will be more or less soft, slightly swollen, and will tear easily. If the condition is very much localized, cysts filled with mucin may be found. Three substances closely related are included under the heading of Myxomatous Metamorphosis: *mucin*, *pseudomucin*, and *paramucin*, each one differing slightly from the others in its reaction.

The typical mucoid cell is the so-called "goblet-cell" that is found in the large intestine.

The mucoid change looks under the microscope very much like edema. The cells are widely separated and the structure of the tissue is poorly defined. The cells frequently stain poorly and degenerate.

**Colloid metamorphosis** is the transformation of the cell substance into a thick, sticky substance known as colloid. It is found only in epithelial cells. It is not precipitated by acetic

acid or by alcohol, nor does it swell in water. It usually stains orange color with Van Gieson.

It is normally found in the acini of the thyroid gland and in the pituitary body. It is frequently found in parovarian cysts, in goiter, in the tubules of the kidney in chronic nephritis, and in the prostate gland.

In cysts the colloid material is generally contained in many small cavities, giving rise to a honeycomb appearance. It may

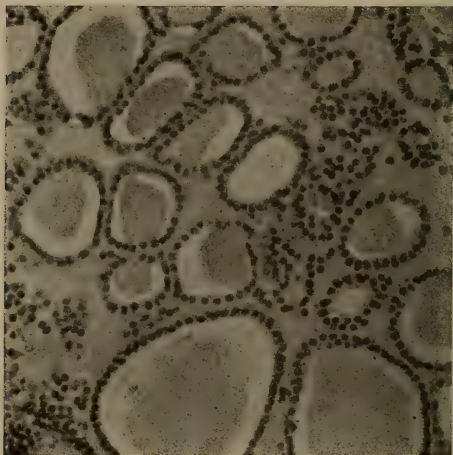


FIG. 9.—COLLOID DEGENERATION OF THE THYROID GLAND, SHOWING MASSES OF COLLOID MATTER IN THE GLAND ACINI (Karg and Schmorl).

be transparent, yellowish, bluish, or chocolate color, according to other substances present.

**Amyloid metamorphosis** is a degeneration of the connective tissues into an abnormal substance giving an amyloid reaction. The origin of this material is obscure. It may be formed *in loco*, but more probably is brought to the tissue from some other part of the body. It does not exist as such in the blood, but is very probably derived from substances contained in that fluid. Some believe that the leukocytes, others that the erythrocytes; are the cells from which it is derived.

It is frequently called *waxy*, *lardaceous*, or "*bacony*" disease; is found in the intercellular portions of the connective tissues and not in secreting cells.

It is found as a result of long-continued suppuration and ulceration, such as occur in diseases of the bone, chronic tuberculosis, syphilis, leukemia, and dysentery.

The organs most commonly affected are the spleen, liver and kidney, the larger blood-vessels, the mucous membrane of the intestines, the lymph-nodes, and the heart.

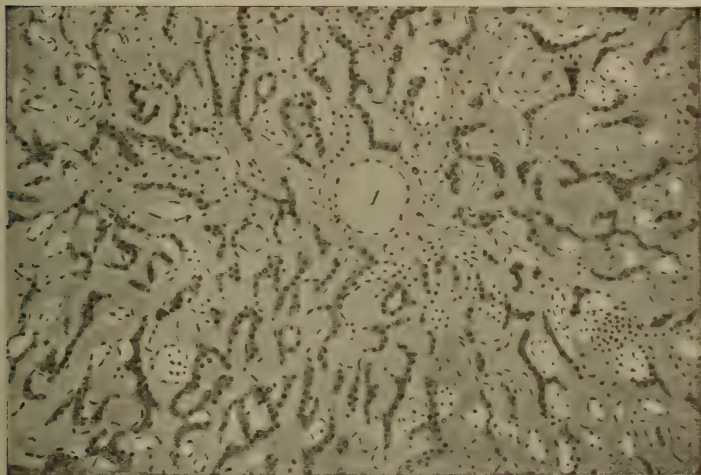


FIG. 10.—AMYLOID DEGENERATION OF THE LIVER.  $\times 98$  (Dürck).

1, Central vein. Portal capillaries surrounded by homogeneous masses and bands; the epithelial lining distinct. Columns of liver cells compressed to narrow, atrophic strips.

The involved organs are generally pale, larger, firmer, and heavier than normal, and with rounded edges. The cut surface is smooth, glistening, and transparent, either diffuse or localized. The usual sites of the degeneration are the walls of the capillaries, in the intima and media, the adventitia being rarely affected.

In the kidney the capillaries of the glomeruli are first at-

tacked, converting the bodies into waxy, homogeneous masses; finally the connective tissue may be involved.

In the liver the amyloid substance is found between the periportal connective tissue and the central vein, in the intermediate zone which is supplied by arterioles and capillaries of the hepatic artery. In the spleen it may give rise to the "sago spleen," a condition which is brought about by the formation of amyloid material in the Malpighian bodies. Later on, the organ may become very extensively involved. In some cases the vessels in the trabeculæ of the organ may be the seat of the metamorphosis.

When amyloid material has been once deposited it is practically never removed. It is insoluble in water, alcohol, ether, dilute acids, alkalis, etc. Resists peptic digestion and withstands decomposition for a long time. Unless special staining methods are employed, it frequently cannot be distinguished from hyaline degeneration.

When the affected tissue is placed in Lugol's solution (iodin 1, potassium iodid 2, water 100) the amyloid substance becomes a mahogany brown. If stained in 5 per cent. aqueous gentian-violet the amyloid will appear pink; the normal tissues, blue.

If after staining in iodine, weak sulphuric acid (5 to 10 per cent.) is added, the amyloid will turn blue.

*Corpora amylacea*, or amyloid bodies, are found in the prostate gland, in lymphatic nodes, and in the central nervous system. They are concentrically striated like a starch granule, and although in their reaction they may resemble starch and amyloid, they are probably neither.

**Glycogenic infiltration** is a deposit of glycogen within the cells. It is found normally in small amount throughout the body except in the mammary glands and central nervous system.

It is greatest in amount in the cells of the liver, in voluntary muscles, and in the kidneys; is also present normally in the blood, both in the plasma and in the cells, particularly the polymorphonuclear leukocytes. It is also commonly found in malignant tumors of mesodermic origin (sarcomata).

The origin of the glycogen is not clear; it is a carbohydrate, but seems to be derived from protein and carbohydrate sub-

stances. Glycogen is most frequently found in the condition known as diabetes.

Tissues containing large amounts of glycogen may have a distinct hyaline appearance. The reactions, however, differ, as it is soluble in water, but not in alcohol, ether, or xylol; is colored a brownish red on the addition of tincture of iodine 1 part, absolute alcohol 4 parts. The brown is not changed to blue on the addition of sulphuric acid.

Microscopically, glycogen occurs in the cells in clear, colorless droplets, usually near the nuclei.

**Serous or edematous infiltration** is a condition of dropsy of the cells. All kinds of cells may be involved, but it is most common in the epithelial. It is an absorption of an excess of plasma by the cells.

It may accompany general dropsy or result from inflammation; is also found in tumors.

The part involved is usually enlarged, spongy, and edematous.

The cells are distended and filled with large and small vacuoles in the protoplasm and at times within the nucleus.

**Pigmentary infiltration** is the deposit of pigment within the tissues.

According to their origin, pigments may be divided into four classes:

1. Those derived from outside of the body.
2. Those formed from hemoglobin and its derivatives, the hematogenous pigments.
3. The hepatogenous or biliary pigments.
4. Metabolic pigment; that resulting from cellular activity within the body is known as melanin.

The *hematogenous* pigments are three—*hemoglobin*, *hemosiderin*, and *hematoidin*.

*Hemoglobin* is dark red in color, amorphous, contains iron, and is soluble in alcohol, ether, and chloroform. It is recognized chemically by the addition to the suspected fluid of a few drops of a fresh tincture of guaiac and then followed by an ethereal solution of hydrogen dioxid. The mixture, which is at first milky white, turns a deep blue.

If the dried blood is dissolved in normal salt solution, then warmed and evaporated, glacial acetic acid added and warmed, small reddish-brown rhombic plates of hemin appear.

When brought in contact with sulphuretted hydrogen, hemoglobin combines and forms ferrous sulphid, which is black. This gives rise to the bluish discoloration of the abdominal wall that appears when decomposition has occurred.

Hemoglobin is set free from the erythrocytes through hemolysis, either within the vessels or when the blood has escaped into the tissues. The surrounding structures will be diffusely stained. This is commonly seen postmortem, particularly in those parts of the liver that are in contact with the intestines. When it is set free within the vessels during life, it may be deposited within the lymph-nodes, spleen, and kidney, forming pigment metastases.

*Hemosiderin* is yellowish or brownish in color, amorphous, contains iron, and is insoluble in water, alkalis, alcohol, ether, xylol, and chloroform.

On the addition of potassium ferrocyanid and weak hydrochloric acid it turns blue (Prussian blue reaction).

It occurs in the blood, in cells and intercellular tissues, as a consequence of recent hemorrhages; apparently results from the slow destruction of the erythrocytes.

The granules are taken up by the phagocytes and may be finally removed by them. Cells filled with the granules are frequently found in the sputum in cases of chronic congestion of the lungs.

*Hematoidin*, similar to bilirubin, is a reddish-brown pigment, found in the form of rhombic crystals; does not contain iron, is insoluble in water, alcohol, or ether, but is soluble in chloroform. It is found at the seat of old hemorrhages, and is generally considered a later form of hemosiderin.

The *causes* of hematogenous pigmentation can be divided into local and general.

*Local*.—Hyperemia, venous stasis, inflammation, hemorrhage.

*General*.—Hemolysis resulting from animal poisons, bacterial toxins, chemicals. Action of parasites, as in the destruction of the red cells in malaria.

*Hepatogenous pigmentation* is due to the presence of pigments derived from the bile, *bilirubin*, which is similar to hematin, and its oxidation product, *biliverdin*. The bilirubin is formed by the hepatic cells from hemoglobin, from destroyed red blood-cells, the iron being retained in the liver and not cast off along with the pigment. It is soluble and consequently is taken up by the blood and carried throughout the body, giving rise to the discoloration known as *icterus* or *jaundice*. Both cells and intercellular substances may be diffusely stained, or, if the condition is of long standing, greenish-yellow crystals or granules may be found.

The fluids of the body will also be discolored.

The presence of these pigments can be recognized by *Gmelin's* test with fuming nitric acid, which will give a play of colors at the point of contact.

This condition may be caused by (1) obstruction to the outflow of bile through the ducts, *obstructive jaundice*; (2) possibly through excessive bile formation resulting from hemolysis, *hematogenous jaundice*; (3) hepatic disorders, as acute yellow atrophy of the liver.

*Metabolic pigmentation* or *melanosis* is a discoloration of the tissues through the formation of *melanin* by the cells.

The tissues are colored yellow, brown, or black.

Under the microscope melanin occurs as dark granules in the cells and intercellular tissues. Is normal in the pigmented cells of the retina, choroid, hair, and skin.

Its chemistry is not well known. It contains sulphur, but little or no iron, is insoluble in water, alcohol, and ether, but soluble in boiling alcohol, acids, and alkalis.

It is found commonly in the *melanotic sarcoma*. It generally tends to destroy the cells in which it is contained, and for some reason such tumors are generally more rapidly metastatic and fatal than the non-pigmented forms.

In *Addison's disease* there is a general bronzing or melanosis of the skin. In many cases this condition seems to follow extensive disease of the adrenals.

In *malaria* the pigment present is probably not melanin, but

is similar to hematin, and is formed by the action of the malarial parasite upon hemoglobin.

Certain *muscular degenerations*, as in "brown atrophy" of the heart. Is questionable whether such granules are true melanin. Various *skin affections*, as freckles, or *lentigo*, *chloasma*, and also in *pigmented moles*.

*Extraneous pigmentation* results from the introduction of coloring-matters into the body from the outside. The tissues

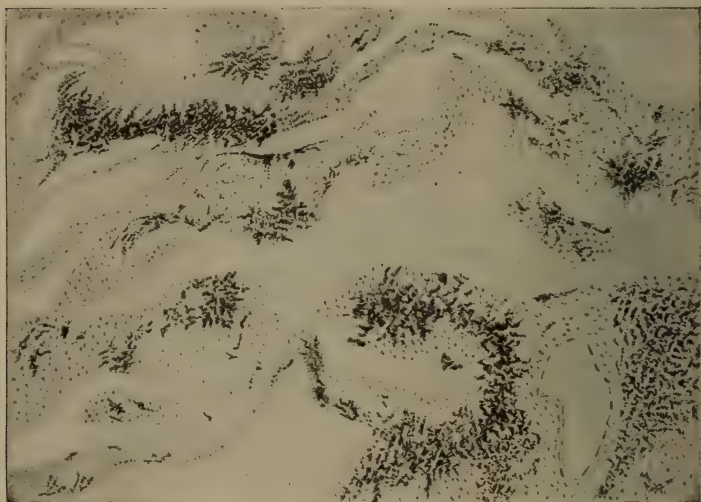


FIG. 11.—ANTHRACOSIS OF THE LUNG.  $\times 100$  (Dürck).

The lung tissue is very much indurated as the result of newly formed connective tissue in which are embedded star-shaped masses of fine, granular, blackish pigment of inhaled coal particles.

most commonly affected are those of the lungs, giving rise to the condition known as *pneumonokoniosis*.

*Anthracosis*, or the deposition of coal-dust, is the most frequent, the lung being colored more or less black according to the amount present.

*Siderosis* results from the inhalation of fine particles of iron.

*Chalcosis*, caused by the presence of lime in the lungs.

*Argyria* is a bluish-gray discoloration of the skin resulting from the long-continued use, internally, of nitrate of silver.

*Tattoo marks* following the introduction of insoluble coloring substances into the skin.

**Calcareous infiltration** or **calcification** refers to the deposit of earthy salts within the tissues. It occurs in consequence of a deficiency of oxygen and an excess of carbon dioxid in the tissue

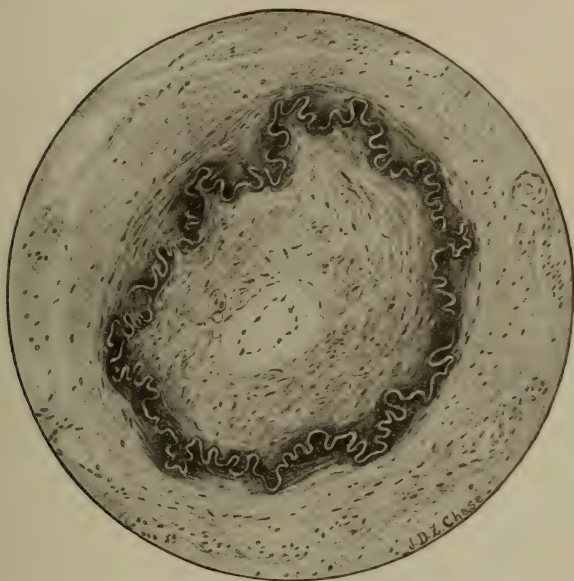


FIG. 12.—CALCAREOUS INFILTRATION OF THE WALL OF A SMALL ARTERY FROM THE WALL OF A GUMMA OF THE LIVER. Zeiss, Oc. 2; ob. D. D. (McFarland).

In addition to the calcification that has occurred in the media contiguous to the fenestrated elastic layer, there is marked syphilitic endarteritis with great reduction in the caliber of the vessel from proliferation of the sub-endothelial tissue of the intima.

juices, which causes a deposit of the carbonates and phosphates of magnesium and calcium. Oxalates are also generally present.

This process is found only in those tissues that are either completely destroyed or else undergoing degeneration as a result of imperfect nutrition.

The deposition of the salts is probably due to a lack of oxygen and an increase of carbon dioxide in the tissues, on account of which there is a precipitation of the magnesium and calcium carbonates and phosphates.

It is commonly seen in the fibrous framework, but may be found within the cells as well. The favorite site is in the connective tissues that have a poor blood-supply, such as cartilages, the walls of blood-vessels, also in old inflammatory areas, in regions of degeneration, such as infarcts, around foreign bodies, and in tumors, particularly in degenerated uterine fibroids. Is sometimes seen in the ganglionic nerve-cells, in the "pearls" of epitheliomata, and in the tumors of the nervous system called *psammoma*, which are made up of masses of salts deposited in the tissues. The most common seat is probably in the arterial system. It is often the sequel of a senile atrophy of the elastic tissue of the vessel wall, along with degeneration of the connective tissue and a general fibrosis.

The valves of the heart frequently undergo calcification, as well as the walls of the aorta, the coronary, and cerebral arteries.

Microscopically the salts may appear as granules, spicules, plates, or crystals.

If within the cellular protoplasm the granules may be so numerous as to hide the nucleus.

The salts are insoluble in ether, but give off carbonic acid gas when dissolved by hydrochloric acid. They also stain very deeply with hematoxylin.

*Uratic infiltration* in the form of sodium biurate occurs in the cartilages and fibrous tissues in gout. Ordinarily the above salt is soluble in the blood, but under certain constitutional conditions it is deposited as an insoluble salt. These collections are called *tophi*, and are found particularly in the joints. An admixture of calcium and magnesium carbonate and phosphate is usually present.

**Necrosis** is the death of a part of a living organism. It is the death of a part as distinguished from the death of the entire body (somatic death). The causes of necrosis are (1) *local injury*, (2) *vascular obstruction*, and (3) *trophic disturbances*.

Under the local injuries are included those that are mechanical, chemical, thermal, and bacterial.

*Mechanical* injuries may cause destruction of the cells directly or by interference with the blood-supply. Pressure of foreign bodies will often bring about necrosis.

*Chemical* substances such as the acids and alkalis may cause destruction of the tissues.

*Thermal* injuries, those from extreme heat or cold, will more or less quickly destroy the vitality of the cells.

*Bacterial* products acting as toxic agents will frequently cause necrosis and gangrene.

If vascular obstruction take place suddenly, the nutrition will be shut off and necrosis result.

Trophic disturbances will lessen the resisting power of the tissues with subsequent necrosis. This is seen in decubitus or bed-sore that occurs in various forms of spinal disease. The perforating ulcer of the foot is another example.

The cells in the necrosed areas will show different stages of disintegration. The cell wall may remain, but the cytoplasm will not stain. There may be complete destruction and breaking down of the cell. The granules in the protoplasm disappear, and it in turn becomes cloudy, gradually breaks up, and vacuoles form. The nucleus may lose its staining power or may undergo destruction in one of two ways: By *karyorrhexis*, a breaking down of the chromatin into granules, or by *karyolysis*, a liquefaction of the nuclear constituents.

Necrosis may be of different varieties.

*Coagulation necrosis* is a form of death of those tissues freely supplied with lymph, accompanied by a consolidation of the protein contents. It is a change similar to the coagulation of the blood. The fibrin ferment present acts upon the fibrin factors and fibrin is formed.

It is found in thrombi, blood-clots, and interstitial hemorrhages.

Occurs in various inflammatory exudates, particularly in croupous pneumonia and diphtheria, and in infarcts.

The seat of the necrosis is firmer and paler than normal,

and dry. Later on it may become softer and discolored as a result of disintegration of blood.

*Caseous necrosis* is a condition in which the tissues have been transformed into a cheese-like substance.

It is found only as a sequel to pre-existing coagulation necrosis. Is found most commonly in tuberculosis, but occurs in tumors and in syphilis.

Surrounding the area of caseation there is generally a zone of coagulation.

*Liquefaction* or *colliquation necrosis* is the death of the tissues with liquefaction. It occurs in those tissues that contain little protein substance, especially in anemic infarcts of the brain. The nervous tissue undergoes a softening, becomes semi-fluid, and eventually liquid, remaining as a colliquation cyst.

*Focal necrosis* is a condition in which minute areas of necrosis scarcely visible to the naked eye occur, particularly in the lymph-follicles and the liver in various forms of severe infection. They may be due to minute thrombi or to alterations in the endothelium of the capillaries.

**Gangrene** may be of two forms—dry and moist. The tissues involved are those that are exposed either directly or indirectly to the atmosphere.

*Dry gangrene*, or *mummification*, is the death of tissues with subsequent drying. It occurs particularly in the extremities of old people or of those who are much debilitated. Is generally due to some obstruction of slow formation of the arterial system, by a thrombus, an embolus, by disease of the walls, by a spasmodic contraction of the vessel, or by pressure from the outside. It is usually circumscribed, there is very little odor, the tissues become almost black and mummify through evaporation of the moisture.

*Moist gangrene* is the death of living tissues plus an infection by bacteria that are capable of producing putrefaction.

It occurs in those parts that are exposed to the air, either directly or indirectly.

It takes place in people who have previously been in good physical condition, usually being the result of extensive venous obstruction combined with a weak arterial supply.

The part involved undergoes necrosis and afterward becomes infected. It becomes greenish black, gas blebs appear



FIG. 13.—SENILE DRY GANGRENE OF THE LOWER EXTREMITY, SHOWING LINE OF DEMARCATION (Hektoen).

on the skin or in the tissues, and an extremely offensive odor develops.

The cells break down completely, hemorrhage takes place as a result of destruction of the blood-vessels, and many toxic

substances are formed. They resemble the alkaloids and may bring about marked disturbances of the organism. This form of gangrene may terminate in several ways.

The dead tissue, *sphacelus* or *slough*, gives rise to a zone of inflammation, which is known as the *line of demarcation*, at the point of contact with the healthy tissue. This zone, as a rule, indicates the limits of the gangrenous process. At this site there is a constantly increasing interval between the dead and living tissue. The tissues here break down and form the *line of ulceration*. It is an attempt of nature to throw off the foreign substance and at the same time to form new tissue. The process is known as *exfoliation*. If the necrotic tissue cannot be thrown off, as is the case when bone is involved, there will probably be a *sequestrum* formed. This is the result of new bone forming around the dead tissue before there has been time for it to exfoliate.

If the degenerated area cannot be discharged, as when the internal organs are involved, it frequently becomes surrounded by a capsule of connective tissue that protects the neighboring parts—process of *encapsulation*. Again, the necrotic tissue may disappear through *absorption*, may *calcify*, or undergo *cicatrization* or *organization*.

**Fat necrosis** is a peculiar type occurring usually in the fat within the abdominal cavity. In nearly all cases it seems to be dependent upon some disease of the pancreas, particularly hemorrhagic pancreatitis.

It is the result of the splitting of the fat molecule into its fatty acid and into glycerin. The fatty acids are deposited as crystals and unite with calcium to form salts.

These areas are generally about the size of a pea, whitish in color, soft or gritty. A zone of inflammation may or may not surround them.

**Death** is the cessation of life—meaning that all the component parts of the organism cease to live.

Up to a certain time the cells of the body are able to supply all the needs, but eventually the natural term of life is reached and the cells gradually fail to support the tissues. Such a condition would be termed *physiologic* death. If, however,

it follows as a result of diseased processes, it would be *pathologic*.

The two, however, cannot be strictly separated, as in old age there are always conditions present that are not normal.

The conditions absolutely necessary for life are a continuation of *circulation*, *respiration*, and *innervation*.

There may be a destruction of certain portions of the body without death following, but a cessation of any of the above-mentioned functions brings about dissolution. This is known as *somatic* death, and, according to which function ceased, it is said to have taken place by *syncope*, *asphyxia*, or *coma*.

*Molecular* death refers to the death of cells.

*Signs of death* are those that indicate that the organism has ceased to live. Cessation of the necessary functions may give rise to *apparent* death, but without other indications it cannot be diagnosed with certainty.

The necessary signs are:

*Algor mortis*, a fall of the temperature to that of the surrounding atmosphere. Following tetanus it may, however, be preceded by a distinct rise, continuing for some hours.

*Livores mortis*, or *postmortem lividity*, are the discolored areas that appear in the dependent portions of the body as a result of the dilatation of the blood-vessels. It is often of great importance to distinguish this condition from the discoloration following a blow. In the first the color will disappear on pressure, but in a bruise it will remain, as the blood is not within the vessels.

*Rigor mortis*, or *postmortem rigidity*, is a stiffness due to the coagulation of the albumin of the muscles with the formation of myosin. It is first seen in the muscles of the neck and jaws, then extends downward, involving the entire body.

It generally comes on within four to twelve hours, but may appear immediately or be delayed for twenty-four hours. At the end of twenty-four to forty-eight hours it usually passes off.

If death has occurred suddenly and the individual is in good health, it appears much more quickly than when death has taken place slowly.

*Decomposition* is the infallible sign. Its appearance depends upon the surrounding temperature, taking place more quickly in hot weather. It is first noticed as a greenish discoloration of the abdominal wall, and is due to the sulphuretted hydrogen from the intestines acting upon the iron contained within the hemoglobin.

The tissues soften and there is more or less odor, due to the formation of various gases.

*Loss of elasticity, relaxation of the sphincter muscles and loss of transparency of the cornea, and dilatation of the pupils* complete the list.

Apparent death may occur in hysteria, catalepsy, submersion, cholera, exposure to cold, and action of electricity. It is detected by the absence of the signs of true death. The tissues will appear reddish if a light is held behind them, blood will flow from a wound, moisture will collect on a mirror held in front of the face, and the muscles will react to electricity.

## CHAPTER V

### CELL DIVISION

As a result of the tissue injury in disease, repair is brought about by cell multiplication or reproduction. The extent of this regeneration depends upon the degree of specialization of the tissue.

**The Cell.**—The adult cell consists primarily of a mass of *protoplasm* or *cytoplasm* surrounded by a limiting membrane called the *cell wall*, and containing a *nucleus* within which there may be a small body called the *nucleolus*.

The *cytoplasm*, which is a semifluid substance, is divided into two portions—the *spongioplasm*, which consists of a very elastic and extensible framework, and the *hyaloplasm*, which is homogeneous and less active.

Embedded in the cytoplasm are minute granules known as *microsomes*. These are most numerous toward the center of the cell; the peripheral zone, called *exoplasm*, not containing them.

Foreign bodies and vacuolations may also be found within the cell.

The arrangement of the constituents of the cytoplasm varies at different times. Frequently the spongioplasm is arranged as a distinct reticulum. This is, however, not permanent, and seems to depend upon the relative proportion of the hyaloplasm.

The *nucleus* is confined by a distinct wall, the *nuclear membrane*, within which is the nuclear substance or *karyomitome*. This is divided into a framework of fibrils, the *nuclear fibril*, and an interfibrillar substance, the *nuclear matrix*.

The fibrils consist of a part called *chromatin* or *nuclein* that has a marked affinity for nuclear stain. This portion is supported by fine fibrils of *linin* that do not stain.

There is also present a semifluid substance known as the *karyoplasm* or *nuclear juice*.

The *nucleolus* lies within the nucleus and consists of a substance known as *pyrenin*. Just what is its function is not known. It probably has a distinct purpose during cell multiplication, as it disappears during the division of the nucleus, but reappears when the new nucleus is formed.

Another body, the *centrosome*, is also sometimes found. It is a small, highly refracting body, situated within the nucleus.

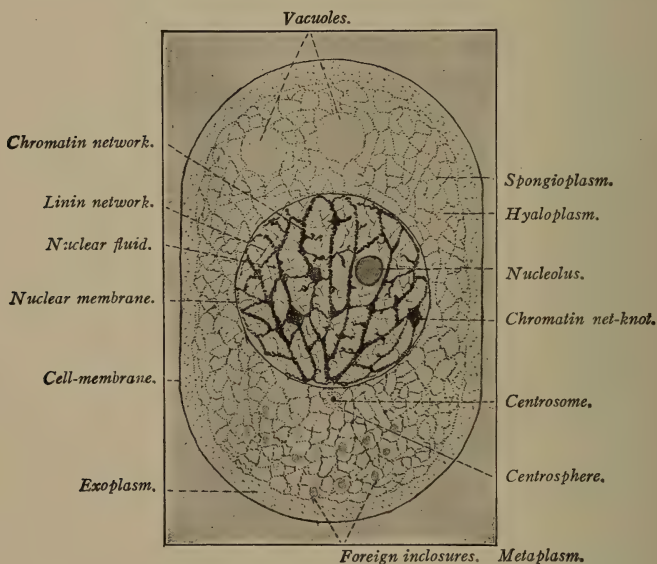


FIG. 14.—DIAGRAM OF A CELL (Huber).

It is surrounded by a clear area called the *attraction sphere*. This body, although it may be found during the stage of rest, becomes most noticeable during the stage of division of the nucleus. At that time it divides into two and passes to opposite poles of the cells.

Occasionally a small irregularly spheric body, the *para-nucleus*, is present in the cytoplasm near the nucleus. Its function is not known.

The relation between the size of the nucleus and that of the cell varies greatly. In certain cells, as in the lymphocyte, the nucleus may occupy nearly the entire area.

The nuclei of the same kind of cells are usually similar in shape and size. They may be round, oval, or, as in some of the lower animals particularly, irregular. The shape of the cell depends partly on environment, partly on specialization.

A cell may also have one or more nuclei, the latter being known as *giant cells*.

With the exception of the red blood-corpuscles and the horny layer of the skin, all cells under normal conditions contain nuclei. The absence of a nucleus, therefore, usually denotes the loss of cellular activity.

The **functions of cells** which distinguish living from inorganic tissues can be divided into:

1. *Metabolism*, the power of selecting and assimilating food, anabolism; and the power of casting off excrementitious matter, catabolism.

2. *Growth*, the result of assimilation producing an increase in the size of the cell.

3. *Irritability*, response of the living cell to external influences.

4. *Motion*, which may be of three different kinds. There is a constant passage of a "circulating albumin" from one part of the cell to another. It may be *ameboid*, so called on account of its resemblance to the motion of the ameba. It consists of a streaming of the cytoplasm to one point, giving rise to prolongations or *pseudopodia* extending from the surface of the cell.

*Ciliary* movement is the result of the presence on the surface of cells of minute, hair-like processes, called *cilia*. These are prolongations and specializations of the protoplasm. The cilia keep up a movement like that of a whip-lash, always in the same direction.

5. *Reproduction* is the multiplication of a cell, and may take place in one of two ways, either by direct division, *amitosis*, which is not the common method, or by indirect division, *karyokinesis*, *karyomitosis*, or *mitosis*. The latter is the more usual way.

In *amitosis* or direct division there is first noticed a slight

contraction in the nucleus of the cell. This gradually goes on until two new nuclei are formed. During this period the cytoplasm begins dividing, and by the time the nuclei have migrated to opposite poles, separation has taken place and two new cells have formed.

If the cytoplasm fails to divide, multinuclear or giant cells may arise.

**Karyokinesis.**—In *karyokinesis*, or indirect division, the cell goes through a very complicated course of changes of the various elements, probably the result of definite metabolic processes.

The changes can best be considered under four headings:

1. *The Prophase.*—The centrosome increases in size, passes from the nucleus into the cytoplasm, and divides into two.

Surrounding each centrosome is a mass of fine radiating lines known as the amphiaster. The rays extending from one centrosome to another are arranged in spindle form, the centrosomes being situated at the apices of the spindles. These achromatin rays form the nuclear spindle.

The nucleus has been enlarging and the chromatin increasing, its particles uniting to form a long fuzzy thread. These fibrils become tangled and convoluted and form the *close skein*. The fibrils become thicker, less convoluted, and arrange themselves in irregular loops, forming the *loose skein*. The chromatin now stains much more deeply than normally. These loops finally separate at their peripheral ends and form the *chromosomes*, V-shaped fibrils with their closed ends arranged in a clear space known as the *polar field*.

During the formation of the skeins the nucleolus and the nuclear membrane disappear and the chromatin fibrils lie in the cell protoplasm.

The chromosomes are always present in the same number in the same species, varying from 2 to 50 in various animals; in man being 24.

The arrangement of the fibrils about the polar field constitutes the *mother star* or *monaster*.

2. *The Metaphase.*—Each of the chromosomes undergoes a longitudinal division into two. These filaments, with the

closed end advancing, begin to separate, moving toward their respective poles or centrosomes.

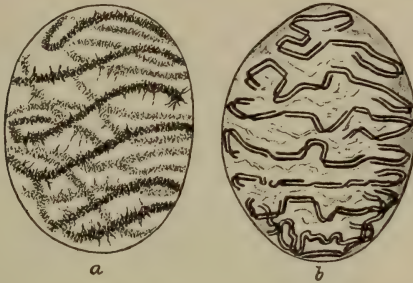


FIG. 15.—NUCLEAR CHANGES IN KARYOKINESIS (Hatschek).

*a*, Nucleus of spermatoblast of *Salamandra maculata*, with chromatin threads forming the first suggestion of a coil; *b*, close coil with disappearance of the fuzzy aspect and longitudinal cleavage of the threads.

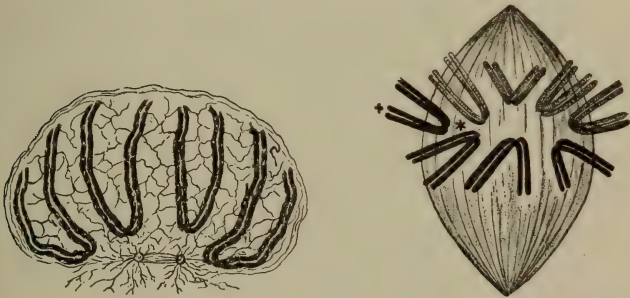


FIG. 16.—DIAGRAMMATIC APPEARANCE OF THE RELATION OF THE CHROMOSOMES TO THE CENTROSOMES AND PRIMITIVE NUCLEAR SPINDLE (Flemming).

FIG. 17.—DIAGRAMMATIC REPRESENTATION OF THE NUCLEAR SPINDLE AND OF THE ARRANGEMENT OF THE DOUBLE CHROMOSOMES IN AN EQUATORIAL PLANE PREPARATORY TO SEPARATION. THIS STAGE IS CALLED THE MOTHER STAR (Flemming).

3. The *anaphase* begins with the migration of the chromosomes. As they move toward the opposite poles the free ends constitute the *equatorial plate*. Connecting the ends are fine threads of achromatin known as the connecting filaments.

The chromosomes collect at the opposite ends and form the *daughter stars* or *diasters*. As this occurs there is the beginning of a constriction of the protoplasm.

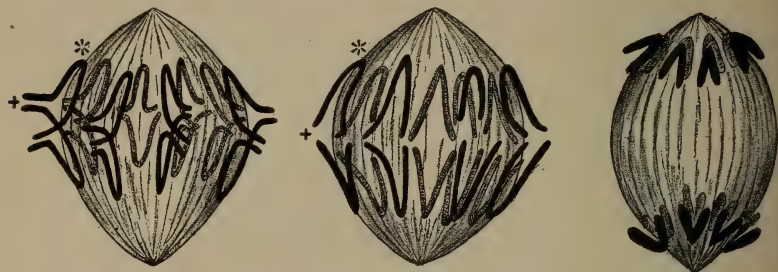


FIG. 18.—DIAGRAMMATIC REPRESENTATION OF THE SEPARATION OF THE CHROMOSOMES, WHICH ARE ATTACHED TOWARD OPPOSITE POLES OF THE NUCLEAR SPINDLE, ABOUT WHICH THEY GATHER TO FORM THE "DAUGHTER STARS" (Flemming).

4. *The Telophase*.—The constriction continues until the original cell has been completely divided and two new ones formed. The chromosomes now undergo in reverse order the

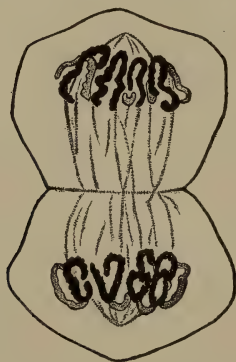


FIG. 19.—SEGMENTATION OF THE CYTOPLASM, AND THE CHROMOSOMES EQUALLY DIVIDED, ABOUT TO FORM NEW NUCLEI IN THE NEW CELLS (Flemming).

phases that have been described: the loose skein, the close skein, the reappearance of the nuclear membrane and of the nucleolus, with finally the stage of rest.

To summarize, the changes are as follows:

*Resting mother nucleus.*

*Prophase.*

Migration and division of the centrosome with increase of chromatin.

Close skein.

Disappearance of the nuclear membrane.

Disappearance of the nucleolus.

Loose skein.

Separation of the skein into chromosomes.

Appearance of the polar field.

Rearrangement of the chromosomes around polar field.

Monaster, or mother star.

Appearance of the nuclear spindle.

*Metaphase.*

Longitudinal division of the chromosomes.

*Anaphase.*

Migration of the divided chromosomes to opposite ends of the cell.

Formation of the equatorial plate.

Diaster or daughter star.

*Telophase.*

Constriction of the protoplasm.

Daughter skeins undergoing in reverse order the above changes.

The stage of rest.

In some instances, instead of the cytoplasm dividing when cleavage of the nucleus is completed, it remains unchanged. This may go on until there are many nuclei, imbedded within a single mass of cytoplasm. Such formations are known as *giant cells*, and may be the result of division under unfavorable circumstances.

There may be the formation of more than two centrosomes with a resulting multipolar cell. The equatorial segments may split up more than once and the daughter cells may divide secondarily.

## CHAPTER VI

### INFLAMMATION AND REGENERATION

**Inflammation** is the protective reaction of irritated and damaged tissues which still retain vitality.

**Etiology.**—The causes of inflammation may be divided into *mechanical*, *chemical*, and *vital*, or *infectious* and *non-infectious*.

Traumatism of any nature, such as a blow or the action of chemicals, can give rise to an inflammatory reaction and be non-infectious.

The common cause, however, is the action of *bacteria* upon the tissues. The great majority, therefore, of inflammations are infectious or vital in variety.

A non-infectious one may become infectious through a secondary deposit of bacteria.

An infectious inflammation is distinguished by the fact that it is likely to be progressive, is capable of indefinite increase, and may also be transmitted from one individual to another.

Before taking up the pathologic changes of the circulation it will be necessary to first consider the normal differences in the blood-current in arteries, veins, and capillaries.

In *arteries* the stream is not constant; it is regularly intermittent on account of the rhythmic contractions of the heart. It is more rapid than in the veins; the red cells cannot be distinguished at the height of systole, but at the end of the heart's action the current slows sufficiently for them to be seen. The corpuscles occupy the entire lumen, except that at the end of the pulse-wave they momentarily withdraw from the wall of the blood-vessel.

In *veins* the stream is constant and is regular in speed. Instead of cells and plasma being uniformly mixed there are two zones present: an *axial* or central zone, composed of blood-

cells, and a *peripheral* one, made up of the blood-plasma. In this latter there are occasionally a few leukocytes, but no erythrocytes found.

In *capillaries* the current is neither constant nor regularly intermittent. It is constant during the flow.

The *changes in the circulation in inflammation* are as follows:

1. A momentary *contraction* of the blood-vessel following the introduction of the irritant. This is followed by:

2. A marked *dilatation* and *relaxation* of the vessel with at first an increase in the rapidity of the flow. Arterioles are first affected, then veins and capillaries.

3. Further increase in dilatation with *slowing* of the current. Instead of the cells being unrecognizable in the arteries,

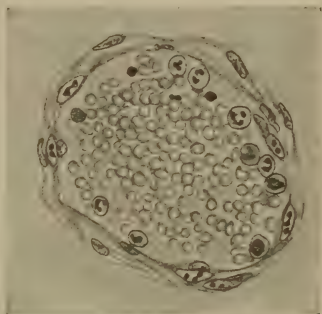


FIG. 20.—ACUTE INFLAMMATION (Mallory).

Peripheral arrangement of polymorphonuclear leukocytes in vein.



FIG. 21.—INFLAMMATION OF THE MESENTERY, SHOWING OVERFILLING OF THE BLOOD-VESSELS, WITH EMIGRATION OF LEUKOCYTES AND DIAPEDESIS OF RED CORPUSCLES (Ziegler).

they now become distinctly visible. Marked changes now occur, particularly in the venous circulation. The plasmatic

zone, which at first contained only a few leukocytes, shows an increase in their number until it is entirely filled with them.

Subsequent to this there takes place an exudation of fluid and blood-cells from the vessels.

*Emigration or Transmigration of the Leukocytes.*—At first the leukocytes adhere but slightly to the walls of the blood-vessel, assuming a pear shape, the enlarged ends pointing in the direction of the current. In the course of five or six hours all the small veins of the involved area may show a mass of leukocytes along their walls. These in time become closely attached, pass through the vessel walls, and, finally, may become *pus cells*.

As a rule, the greater number of leukocytes that escape are of the polymorphonuclear variety. They project a small mass of protoplasm through the vessel wall. This mass becomes gradually larger until the cell lies outside in the surrounding tissues. This process is known as emigration.

*Diapedesis* refers to the escape of red cells from vessels whose walls show no lesions.

At the same time that the cells escape there is an exudation or out-flow of lymph through the vessel walls. This increased amount of lymph renders the tissue edematous and gives room for free ameboid movement of the leukocytes. Many

are actively phagocytic, many die, while some get back into the lymph-vessels and return to the general circulation.

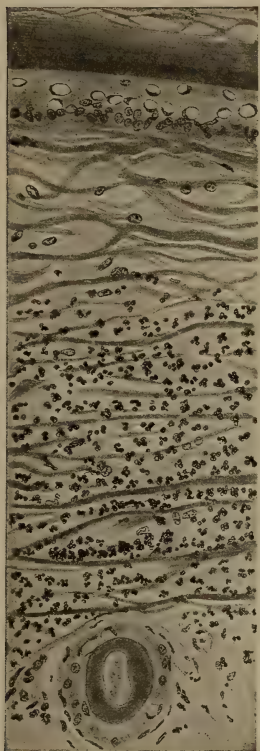


FIG. 22.—ACUTE INFLAMMATION (Mallory).

Emigration and accumulation of polymorphonuclear leukocytes in the subcutaneous tissues of a rabbit's ear as the result of rubbing the surface with dilute croton oil.

As to the emigration of the leukocytes there are various theories, but the reasons are not perfectly understood. The phenomena can hardly be due to nervous influences, as the changes occur too slowly. It is also impossible to bring about an inflammatory reaction by stimulating either the vasoconstrictors or the vasodilators. When the latter is done, there is an exudation of plasma, but not of cells. According to Cohnheim, there is an increased permeability of the blood-vessel wall due to structural changes.

Probably the chief reason is that the ameboid motion of the leukocytes is very much stimulated.

It may also be the result of *positive chemotaxis*, the attraction that certain substances exert upon motile cells. Dead tissues and the products of bacterial growth are positively chemotactic, and their influence may be exerted upon the leukocytes while they are still within the blood-vessel.

Besides the polymorphonuclear leukocyte the round mononuclear form may also escape, giving rise to the *round-cell infiltration* that is found in subacute or chronic inflammation, particularly in tuberculosis and syphilis.

As a result of the disturbances of the circulation there are certain changes in the inflamed part as a whole that are frequently spoken of as the *cardinal symptoms* of inflammation:

*Pain*, or dolor, due probably to the pressure exerted upon the terminal nerve-filaments. Also to the action of toxins, acids, enzymes, etc., upon the nerve-endings.

*Swelling*, or tumor, due to the increased amount of blood present and to the exudate within the tissues.

*Redness*, or rubor, due also to the hyperemia. The increase of blood to the involved part brings more leukocytes, diluents, and antibodies, facilitates the removal of harmful substances, and possibly, in some instances, affords increased nutrition to the cells in that area.

*Heat*, or calor, the result of two causes, one that more blood is brought to the part, the other that the blood moves more slowly and heat accumulates.

*Altered function*, or *functio læsa*, may be added to the first four.

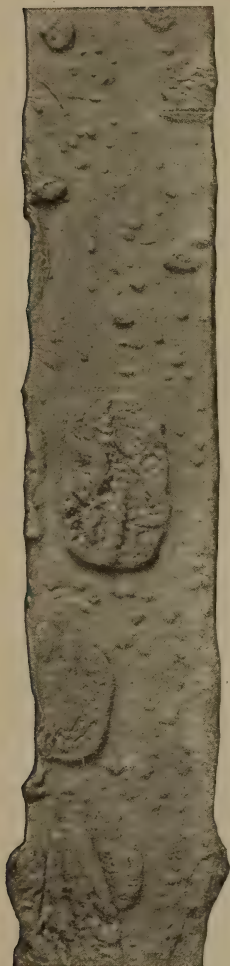


FIG. 23.—ILEUM; TYPHOID FEVER (EARLY STAGE) (Nicholls).

Peyer's patches and solitary follicles greatly swollen; superficial ulceration.

The products of inflammation are known as *inflammatory exudates*.

A *serous* exudate is one that is composed of fluid that has escaped from the vessels. It contains few cells, occurs in very slight inflammations, and tends to coagulate spontaneously.

This fluid differs from the non-inflammatory transudate in containing a greater amount of albumin, and, therefore, being of a greater specific gravity. The amount of exudate depends largely upon the vascularity of the part.

A *fibrinous* exudate is one in which there is more or less fibrin present, which probably helps restrict the escape of the infecting agents. It is formed by the action of fibrin ferment acting upon fibrinogen or fibrin-forming substances in the presence of calcium salts. This ferment is yielded probably to some extent by all the cells of the blood, but particularly by the leukocytes. When they die, the ferment is formed and the fibrinogen is converted into fibrin. When the leukocytes are increased in number, the amount of fibrin is usually greater.

A *purulent* exudate is one in which there is a preponderance of escaped leukocytes. It may be found infiltrating the tissues or in a circumscribed area known as an abscess. This exudate is known as pus.

A *hemorrhagic* exudation is one

that contains erythrocytes. It generally indicates that there has been a lesion of blood-vessels.

*Pus* is an opaque, yellowish, alkaline fluid, specific gravity about 1050. It is made up of pus cells, either living or dead polymorphonuclear leukocytes, and *pus serum* (liquor puris). Usually some degenerated tissue cells are present. According to whether there is blood, serum, or mucus as well, it may be *sanious pus*, *seropus*, or *mucopus*.

If the fluid portion is scanty, the pus may be *creamy* or *cheesy*; or *ichorous* if the pus is very thin, watery, and acid.

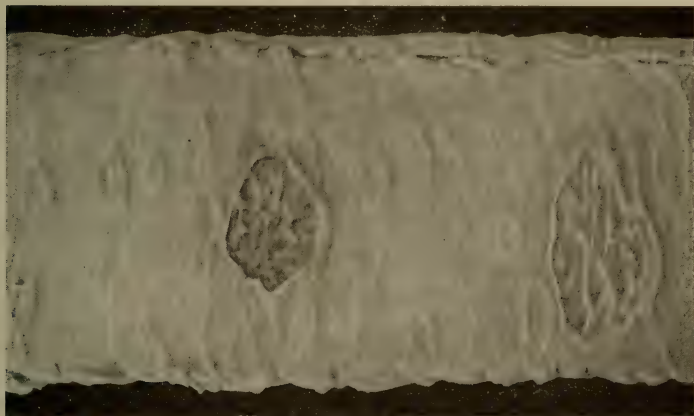


FIG. 24.—TUBERCULOUS ULCERATION OF THE INTESTINE (Stengel).

An *abscess* is a circumscribed collection of pus. It is surrounded by an inflammatory zone incorrectly called a pyogenic membrane.

An abscess may be *hot* or *cold*. The first is the result of acute inflammatory changes. The latter is a chronic inflammatory process, and the fluid contained within it is not pus, but is made up of broken-down and degenerated tissues.

An *embolic* abscess is one that has followed the lodgment of a septic embolus.

*Pyemic* or *metastatic* abscesses are those resulting from pyo-

genic organisms present in the blood becoming lodged in the tissues and causing local purulent lesions.

The various steps occurring in the formation of an abscess due to bacterial infection are as follows: After the pus-producing organisms gain entrance they undergo multiplication without at first causing any reaction. In a very short time, however, the invaded area becomes congested, the leukocytes approach the wall of the blood-vessels, and degenerative changes in the neighboring tissue cells appear. There is a multiplication of the bacteria, the polymorphonuclear leukocytes escape from the vessels, and mononuclear leukocytes (small round cells) collect. The polynuclear leukocytes and other cells, including

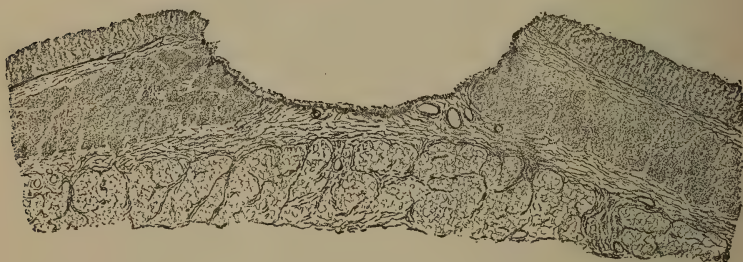


FIG. 25.—CHRONIC ULCER OF THE STOMACH. SHOWING A SECTION THROUGH THE STOMACH WALL AT THE CENTRAL PART OF THE ROUND ULCER (Delafield and Prudden).

endothelial cells, take up large numbers of bacteria. More leukocytes appear until the tissue becomes densely filled by them. This is accompanied by a yet greater proliferation of the bacteria which extend along the lymph-streams into the region outside of the developing abscess. There is now a breaking down of the leukocytes, with the setting free of various ferments and a coincident destruction of the tissue of the affected portion.

The destruction of tissue that accompanies abscess formation is in consequence of there being an insufficient amount of nutrition, and is due also to the dissolving effect of digestive

enzymes present in the liquor puris, probably derived from the broken-down leukocytes.

When the broken-down tissue has been cast off there remains a superficial lesion with loss of substance. This area is known as an *ulcer*.

A *sinus* is an inflammatory tract that is open at one end from which the exudate can escape.

A *fistula* is an inflammatory tract that is open at both ends. It is one that joins an internal cavity to the surface.

The **termination of inflammation** depends upon the degree of inflammation and the amount of damage done. It may occur by *resolution*. This takes place only when the inflammation has been slight. The exudate is taken up by the lymphatics and returned to the circulation. Any degenerated cells will be taken up by the wandering leukocytes and the tissue will resume its normal condition.

In *suppuration* the inflammation has been destructive; there is actual loss of tissue, with the formation of pus.

As pus is formed it is either confined as an abscess or else it tends to infiltrate the tissues. In either case the tissues attempt to get rid of the irritating substance by having it follow along the least resistant paths and letting it escape from the body. This process of extension is known as "burrowing"; it results from the increased pressure due to the presence of the pus and to the digestive powers of the enzymes contained within.

In some cases the pus may quickly escape to the surface of the body and be cast off. It may, however, have to burrow a long distance, as in a psoas abscess, before it can escape.

Sometimes the pus may gain entrance into one of the cavities of the body, as the peritoneum or pleura, and give rise to inflammatory conditions there.

According to the cavity involved, the condition has special names. *Empyema* is pus within a pleural cavity; *pyopericardium* when within the pericardial sac; *pyosalpinx* when a Fallopian tube is involved, etc.

*Encapsulation* is what takes place when the irritating material cannot be removed from the body. The surrounding

tissue cells undergo multiplication and the substance is isolated by the formation of a connective-tissue capsule about it.

*Organization* is the process of repair by means of which the destroyed areas are filled up by connective tissue. It is not a case of the transformation of the inflammatory products into connective tissue, but is a condition of replacing. This new formation of connective tissue is known as a *cicatrix* or *scar*, the process as *cicatrization*.

The cells present in the repair of inflammation are derived from various sources, and consequently differ among themselves.

The *leukocytes* that form the greatest numbers are derived from the blood and are chiefly of the polymorphonuclear variety.

*Lymphocytes* both large and small, as well as *eosinophiles* in small numbers, may also be present.

Eosinophile cells are actively ameboid and are able to escape from the blood-vessels. As a rule, they are not present in marked numbers except in certain subacute or chronic inflammations of the skin or mucous membranes.

The *plasma* cells probably originate from the connective tissue, but may be derived partly from the blood. They are rather large, and contain a pale, vesicular nucleus eccentrically placed and a finely granular basophilic protoplasm. These cells are usually most numerous in acute toxic conditions and are supposed to play some part in the formation of connective tissue.

The *mast* cells or *basophilic leukocytes* are large cells containing usually a trilobed vesicular nucleus and large granules in the cytoplasm. They are most common in inflammations of mucous membranes and in the neighborhood of tumors, especially if they have undergone mucoïd changes.

The *fibroblasts* or *epithelioid* cells are formed by the proliferation of pre-existing connective-tissue cells.

*Giant cells*, those containing more than one nucleus, are frequently present. The formation of these cells probably takes place in one of two ways. If a single cell is not sufficiently powerful to remove the offending particle, several

may coalesce, and in that way successfully make the attack. They may, however, form through a multiplication of the nuclei without division of the cytoplasm.

In the process of *repair* there is formed what is called *granulation tissue* which acts as a strong barrier to absorption and infection. In it there is the formation of loops of new capillaries

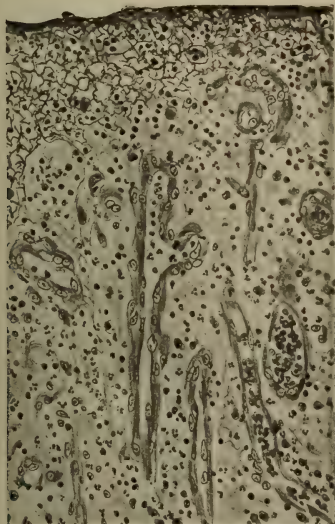
*a**b*

FIG. 26.—GRANULATION TISSUE (Mallory).

*a*, Surface portion, composed chiefly of newly formed blood-vessels; very few fibroblasts; many polymorphonuclear leukocytes between the vessels and in the fibrin on the surface; blood-vessels and leukocytes separated by serum. *b*, Deeper portion; many lymphocytes between blood-vessels; young fibroblasts growing in horizontal arrangement at base.

derived from the endothelial lining of pre-existing blood-vessels. The endothelial cell becomes larger, the nucleus divides by mitosis, and two cells are formed. These cells continue dividing until a sprout-like process extending into the surrounding tissue is formed. Adjoining sprouts unite, and, although at first solid, finally become hollowed out, thus allowing the circulation to be

re-established. At the same time that this is taking place there is a multiplication of the *fixed* connective-tissue cells, which surround and act as a supporting framework to the loops of new-forming capillaries.

In the proliferation of the connective tissue there is first found a small round cell with a round or oval nucleus. As the tissue becomes older the cells tend to elongate and become spindle shaped. At first they are very close together, but gradually separate, and the homogeneous intercellular substance becomes fibrillar and supports the cells. Those cells concerned in the formation of the cicatrix are called *fibroblasts*.

In the new-formed tissue there is at first an overproduction of cells and blood-vessels, but eventually it becomes less vascular and cellular. This is brought about to a great extent by the contraction of the cicatrix, which, at first reddish and elevated, finally becomes pale and depressed.

According to surgeons, cicatrization may take place in one of two ways:

*Union by first intention, or primary union.* In this the edges of the wound are closely brought together and very little exudate escapes. In this narrow space the same processes take place as are seen in the formation of granulation tissue, coagulation, fibrin formation, phagocytosis, and proliferation of capillaries and connective tissue, but to a much less extent. The epithelial surface is replaced by a proliferation of the neighboring epithelium.

*Union by second intention, secondary union, or union by granulation,* takes place when the edges of the wound are far apart and there is a large amount of exudate present.

This process is the same as healing by first intention, except that in it there is supplied the material bridge over the gap.

If an epithelial surface is affected, the granulation tissue is gradually covered by proliferation of adjacent cells.

*Regeneration*, although commonly applied to the formation of cicatricial tissue, really refers to the power of individual tissues to reproduce their own kind.

Generally speaking, the more highly specialized the tissue, the less is its regenerative power. If such tissues are

destroyed, they are generally replaced by fibrous tissue. A cell can give rise in regeneration only to a tissue that has the same blastodermic origin.

The *fibrous connective tissue* is probably the most active.

*Epithelium* of the surface variety is constantly and completely regenerating. Whether regeneration takes place in

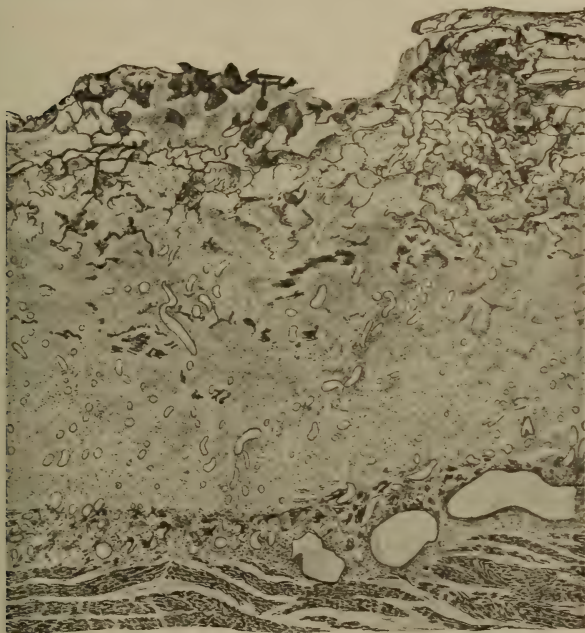


FIG. 27.—HEART. ORGANIZING PERICARDITIS. FIBRIN STILL PRESENT ALONG SURFACE AND BENEATH IT (Mallory).

the more highly specialized epithelial organs, such as the kidney and liver, is rather improbable.

*Muscular tissue* is capable of regeneration to a slight degree, but the chief repair after injury to muscle takes place within the connective tissues surrounding the fibers.

*Blood-vessels*, as is seen in the formation of granulation tissue, are capable of marked multiplication. The new-formed

vessels in regeneration are usually only temporary; existing only long enough for the tissue to receive its nutrition, then disappearing during the contraction of the cicatrix.

*Bone*, as is noticed in the repair of fractures, is able to undergo complete regeneration.

*Cartilage* is incapable of regeneration. In injuries it is replaced by fibrous connective tissue.

*Nerve-cells* of the highly specialized type, such as ganglion cells, cannot regenerate, but the *neuroglia* or nerve connective tissue can. The neuroglia differs from the ordinary fibrous tissue in that it is derived from the ectodermic layer of the blastoderm.

**Varieties of Inflammation.**—Inflammation may be—

*Acute* when it arises rapidly, lasts a short time, and destroys tissue.

*Chronic* when arising slowly, lasting a long time, and giving rise to the formation of fibrous connective tissue.

*Infectious* when caused by some living organism.

*Non-infectious* when it does not arise from the action of a living organism.

*Exudative* if the inflammation is characterized by the presence of an exudate. According to the variety of the exudate, the inflammation may be as follows:

*Serous* when the exudate consists of a fluid having few cellular contents.

*Fibrinous* when particles of fibrin are present in the exudate.

*Purulent* when pus cells (leukocytes) are present in large numbers.

*Hemorrhagic* when erythrocytes escape in quantity.

*Parenchymatous* when the actively secreting cells of a glandular organ are involved.

*Interstitial* if the inflammatory process involves the connective-tissue framework of an organ.

*Catarrhal* when limited to mucous membranes.

In the early stage the secretion of mucus by the cells ceases, the surface becomes dry, and the blood-vessels congested. Later on, the secretion is increased in amount, frequently

changed in character, and the congestion of the vessels somewhat lessened.

*Desquamative* if there is a casting off of epithelium in a catarrhal inflammation.

*Vesicular* when there are larger and smaller circumscribed elevated areas containing a serous exudate, as in blisters.

*Pustular* when the circumscribed elevations contain pus.

*Diphtheric* or *croupous* when there is a marked coagulation of fibrin on the surface with the formation of a pseudo-membrane in which are found degenerated cells of various types—epithelial, leukocytes, and erythrocytes.

In it there is usually necrosis involving the superficial epithelium, or going deeper and attacking the submucosa as well as the mucosa.

*Ulcerative* if accompanied by a loss of superficial substance.

*Degenerative* when the destruction of tissue is extensive.

*Adhesive* when, as the result of the presence of fibrin, replacement by fibrous tissue follows and the two opposing surfaces become more or less adherent, the process being the same as occurs in scar formation. It may go on to the point where the cavity entirely disappears, and is then called *obliterative*.

*Gangrenous* when there has been infection of the tissues by putrefying, saprophytic organisms and gangrene is present.

*Phlegmonous* when the interstitial tissues become infiltrated by pus.

*Productive* when the formation of fibrous connective tissue is prominent.

*Specific* when caused by a definite micro-organism.

## CHAPTER VII

### THE SPECIFIC INFLAMMATIONS (GRANULOMATA)

#### TUBERCULOSIS

*Tuberculosis* is a specific infectious disease characterized by the formation of tubercles.

It is caused by the *Bacillus tuberculosis*, which is non-motile, non-sporogenous, aërobic, acid resisting, and purely parasitic. Occurs as a slender, rod-shaped, slightly curved body, usually with rounded ends, but sometimes showing distinct branches. It is about 1.5 to 3.5  $\mu$  long by 0.25  $\mu$  wide. It is found in sputa and in the lesion of tuberculosis. It is the cause of all forms of tuberculosis in man and may be transmitted to many of the lower animals. It is still unsettled whether the forms found in animals are capable of being pathogenic to man. The bovine bacillus, however, is apparently pathogenic in a small percentage of cases.

*Staining* is difficult, but after having once taken it up, the organism is with difficulty decolorized. Use Ziehl-Neelson method. Stains by Gram's.

**Culture.**—Blood-serum, glycerin agar-agar, potato, and glycerin bouillon. It is difficult to cultivate, growth is slow, best at 37° C., none when below 29° C. or above 42° C. Growth is dry, lusterless, coarsely granular, wrinkled, and slightly yellowish.

**Pathogenesis.**—Tuberculosis results from the successful invasion of the *Bacillus tuberculosis*. This may take place by means of: (1) the respiration; (2) the blood circulation; (3) lymphatic channels; (4) ingestion. After having gained entrance it may give metastases by any of the first three, by continuity of tissue, or by direct implantation.

The characteristic lesion is the miliary tubercle, which is gray in color as long as degeneration and caseation have not

occurred; it then becomes yellow. It is rarely circumscribed by any definite boundary, and it tends to infiltrate and form tubercles in the adjacent tissues. It is a small area of inflammation and degeneration resulting from the action of the bacillus. The primary lesion does not necessarily occur at the point where the bacilli gained entrance. When the organism enters a suitable location, it undergoes multiplication. In a short time their number and the products of their metabolism bring about an increase in the number of fixed connective-tissue cells—epithelioid cells. These cells are the first to appear. A little later, through the chemotactic effect of the bacteria, lymphoid cells escape from the blood-vessels. According to which cell predominates, the tubercle may be either *epithelioid* or *lymphoid*.

As the bacteria multiply, more nutrition is required, but this variety of inflammation is peculiar in that not only no new blood-vessels are formed, but the pre-existing ones are destroyed by endarteritis and thrombosis as the process advances. Consequently, the central area, the older portion, undergoes degeneration and coagulation necrosis.

The tubercle may be divided into three zones, according to its histologic characteristics: (1) A *central* zone containing bacteria and tissue cells that have undergone coagulation necrosis. (2) A *median* zone, in which are many epithelioid cells and frequently giant cells containing vesicular nuclei arranged peripherally and radially. (3) A *peripheral* zone, in which are found a few epithelioid, many lymphoid, and some plasma cells.

The giant cells as well as the epithelioid may come from the endothelium of the blood-vessels or lymph-vessels, from fibroblasts or from escaped leukocytes.

If the process has been rapid, the lymphoid cells usually predominate. If the individual's resistance is fairly good, some of the epithelioid cells may be converted into fibrous tissue. When resistance is marked, the tubercle may become encapsulated by fibrous tissue, and eventually become infiltrated by lime salts. This occurs only where the resisting power of the patient becomes greater than the destroying ability of the organism.

As, however, the bacilli keep continually multiplying, the tendency of the disease is to extend. This occurs by the organisms being carried into the lymphatic channels either directly or by the action of phagocytes. The latter may carry and deposit them in a neighboring lymph-node, where secondary lesions will occur. Metastasis may also take place by the organisms gaining entrance into a vein, entering the general

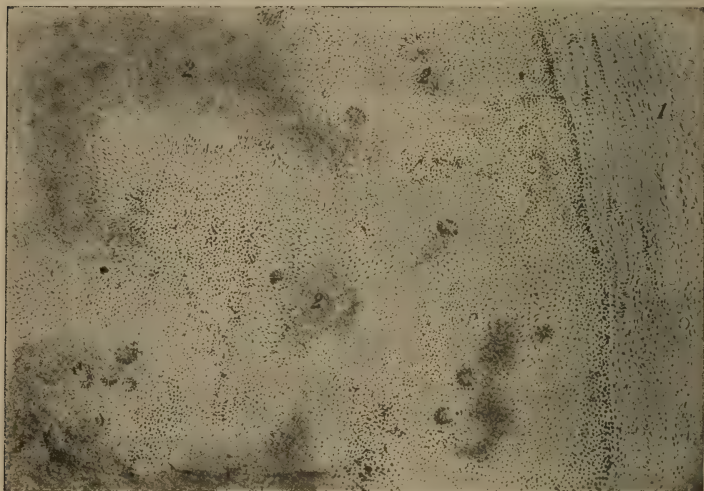


FIG. 28.—SUBACUTE TUBERCULOSIS OF A LYMPH-GLAND.  $\times 70$  (Dürck).

1, Thickened capsule; 2, caseous centers of the tubercles. At the periphery of the gland the tubercles are still discrete, and between them lies lymphadenoid tissue. In the center of the gland the nodules have formed larger confluent areas. Numerous giant cells.

circulation, and setting up a more or less widely diffused general miliary infection.

Recovery from tuberculosis is more common than is generally believed. According to postmortem examinations, 20 per cent. of the cases of tuberculosis recover. In such cases there is present the ability of the individual to resist the inroads of the process. The tubercle bacilli become encapsulated in a mass of connective tissue that prevents their further growth and

extension. This new-formed tissue tends to contract and causes the broken-down portions to be absorbed, or else calcareous infiltration takes place.

These walled-off areas are, however, still a source of danger. Although tubercle bacilli do not form spores, yet infection may take place years after the connective-tissue growth, if for any reason the contents happen to escape.

When it remains quiet it is called "latent" tuberculosis.

The symptoms seen are probably due in a great part to the presence of associated pyogenic organisms. The night-sweats, fever, and loss of weight seen in cases of pulmonary tuberculosis are due to the associated bacteria. There is generally present some anemia, and many authors claim that there is an increase in the number of lymphocytes in the blood.

The liver frequently shows marked fatty infiltration and sometimes amyloid degeneration to a slight or a marked degree, depending upon the amount of suppuration.

The most common entrance for infection is the respiratory system. Sputum from tuberculous patients becomes dried and comminuted; it is then carried about by the currents of air and enters the body.

The intestines may become secondarily involved through infection brought about by swallowing the tuberculous sputum.

Congenital tuberculosis may come from the paternal side from infection of the genitals; from the maternal side through infection of an ovum, or it may be transmitted through the placenta. Heredity is no longer thought to have much direct influence. It is now believed that what is inherited is nothing more than a weakened resisting power.

## LEPROSY

*Leprosy* is a chronic, specific, infectious, inflammatory disease caused by the *Bacillus lepræ*, which is a non-motile, non-sporogenous, acid-resisting, purely parasitic organism. It is pathogenic for man, but some of the lower animals appear to be somewhat susceptible. Is very slightly contagious. Is stained with some difficulty. Stains by Gram's. An acid-fast organism

supposed to be the *B. lepræ* has been grown on artificial culture-media containing split-up nucleoproteins.

It occurs most commonly in warm climates and in people of almost any age. Is most common in males of from twenty to thirty years. It is probably not hereditary, but children under three years have been affected. Infection may be trans-

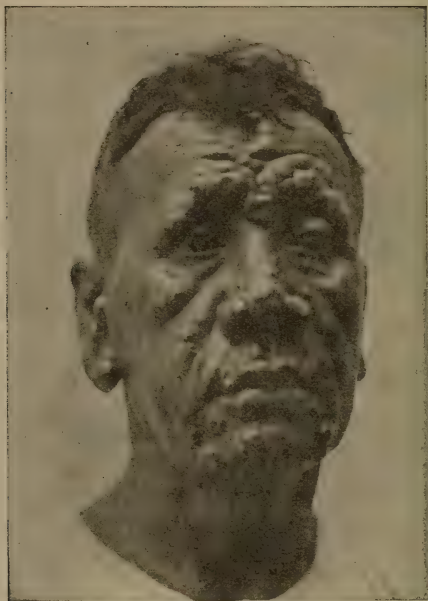


FIG. 29.—NODULAR LEPROSY.

mitted by: (1) direct inoculation; (2) kissing and sexual intercourse; (3) clothing; (4) bites of insects.

The bacilli are distributed to an extraordinary extent in the body of the leper, and in many cases there will be no inflammatory reaction in their neighborhood. They may be either extracellular or intracellular, and in the latter case may be found in giant cells or lepra cells. These may contain numerous nuclei and numbers of vacuoles as well as bacteria.

The secretions of the numerous membranes of the nose usually contain great numbers of the bacilli.

**Varieties.**—Two forms are commonly met with, the *nodular* and the *anesthetic* or *nerve* leprosy. It is seldom, however, that a quite pure case of either is found; the majority belong to the mixed form. In the *nodular* variety the node may be preceded



FIG. 30.—MACULAR LESIONS IN ANESTHETIC LEPROSY.

by a hyperemic patch which leaves behind it a pigmented area. The nodules appear first in the skin and subcutaneous tissue of the face, and may remain single or become confluent.

Macroscopically the nodes are rather grayish or yellowish. Microscopically each node is made up of granulomatous tissue composed of lymphoid and epithelioid cells retained in a loose

connective-tissue network; in these masses the bacilli occur in great number between and in the cells. These lesions are more vascular than those of tuberculosis, and consequently do not tend to undergo coagulation necrosis. Caseation does not take place and the ulceration that is so common depends largely upon injuries and secondary infections.

The nodules are found in other parts of the body, as on the back of the hand,—palm is not usually involved,—in the mucous membrane of the eye, nose, mouth, larynx, and intestines.

The lymph-glands in both varieties are swollen, hard from connective-tissue formation, and yellowish on account of fatty degeneration.

*Anesthetic leprosy* is characterized by the growth of the bacilli in the sheath of the nerves and an increase in the connective tissue along their course. Is most common on the ulnar and popliteal nerves, which at first may be painful. There then appears neuritis with localized hyperemic spots, the nerve affected being red and swollen; later it becomes harder, pale, and gray, with nodular or fusiform enlargements. The neurilemma usually becomes thickened, fibrous, and infiltrated by cells and bacilli. These become anesthetic, and in some cases become the seat of a blister. Finally, ulceration may develop with the subsequent loss of the fingers or toes.

Many of the enlarged nodes may be the result of a secondary tuberculosis occurring late in the course of the disease. There is frequently fever and also nephritis. Amyloid degeneration is not uncommon in the ulcerative forms.

The majority of the cases last from five to twenty years, usually dying of tuberculosis.

### GLANDERS

Is a specific infectious disease of horses that is sometimes seen in man as the result of accidental infection.

Is caused by the *Bacillus mallei*, a non-motile, non-sporulating, aërobic or optionally anaërobic bacillus 2 to 5  $\mu$  in length. Is pathogenic for man and lower animals. Stains by ordinary methods, but not by Gram's. Grows on ordinary media, but best on glycerin agar.

It makes its appearance in the membrane of the nose in horses in the form of small nodules the size of a pea. These may increase in size, but eventually break down and ulcerate, with the formation of irregular ulcers, having yellowish, elevated, and indurated borders from which some bloody pus is discharged. Lymph-nodes become enlarged, and metastatic abscesses may result. The lungs are frequently involved and macroscopically resemble a tuberculous bronchopneumonia.

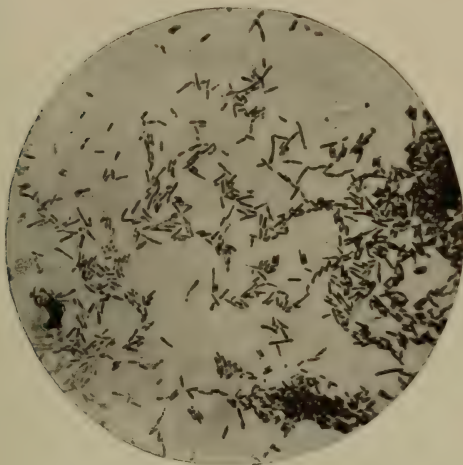


FIG. 31.—*BACILLUS MALLEI*, FROM A CULTURE UPON GLYCERIN AGAR-AGAR.  
× 1000 (Fränkel and Pfeiffer).

Microscopically the nodules consist of masses of small round cells and epithelioid cells. Do not find giant cells.

If the skin is involved the condition is known as "farcy," and the nodules as "farcy buds." They generally undergo central necrosis and suppuration with very extensive ulceration.

Man may become infected through lesions of the mucous membranes of the eye or nose or of the skin, and the result is usually fatal. The course is that of an acute febrile affection suggesting typhoid fever.

## SPOROTRICHOSIS

Is a chronic inflammatory process due to the presence of a pathogenic fungus, formed of sporangia and mycelia, the *sporotrichium*. These organisms are strictly aërobic; grow on the ordinary culture-media at a temperature of 20° to 28° C. They do not stain well, taking the ordinary anilin dyes faintly; if not decolorized too vigorously they stain by Gram's method.

The lesion quite commonly starts at the site of some trifling injury, particularly of the hand. The infected area may or may not become sluggishly inflamed, and there develops a small dermic, sometimes subcutaneous, nodule which may break down and become soft. This may develop into a sluggishly inflamed, discharging sore.

Sooner or later a subcutaneous nodule will be felt at the lower end of the forearm. This gradually enlarges to the size of a cherry, may spread laterally, and finally softens. The overlying skin becomes thinned and of a purplish color, then breaks through, the discharge being of a viscid, gelatinous, seropurulent character. This formation is successively followed by several such nodules higher up the arm along the lymphatic vessels which can be felt usually as hard cords.

Microscopically may conform more or less closely to one of three types, or there may be an admixture of all varieties: 1. Proliferation of the connective tissue with lymphoid cells, syphiloid. 2. Epithelioid proliferation with giant cells, tubercloid. 3. Polynuclear infiltration resembling suppuration.

It may be difficult to find the organism by staining the discharges, but the fungus grows readily on ordinary culture-media.

## ACTINOMYCOSIS

Is a chronic contagious disease of cattle, "lumpy jaw," but is sometimes found in man.

Is caused by a fungus, probably a streptothrix, the *Actinomyces bovis*, which is large enough to be seen by the naked eye, appearing as small yellow particles. The fungus is made up of a central mass of granular substance in which there are many structures resembling chains of cocci or spores. Extending

from this center are many mycelial threads terminating in club-shaped extremities. Is both aërobic and anaërobic in its growth; was formerly thought that the latter form alone was pathogenic. Will grow on any artificial media.

Stains yellow with picric acid, red with picrocarmin, blue with anilin gentian and by Gram's.

The infection is supposed to take place by means of spores gaining entrance into the human system by means of food or by inhalation. Probably enters by way of decayed teeth or through abrasions of the mucous membrane.

Where the fungus lodges there is a formation of nodules which break down, form abscesses, and discharge a creamy pus containing yellowish granules; which show the characteristic rayed appearance when looked at under the microscope.

The neighboring bones may become riddled with sinuses and there may also be metastatic growths in other organs, particularly the lungs. In the latter extensive necrosis may occur, with the formation of small cavities containing pus and fragments of degenerated tissues, and the fungus will be found in the sputum.

Instead of breaking down, connective tissue may be formed and encapsulate the invaded area.

Microscopically there is found a granulation tissue containing large masses of lymphoid cells, a few epithelioid cells, and giant cells resembling closely a tubercle.

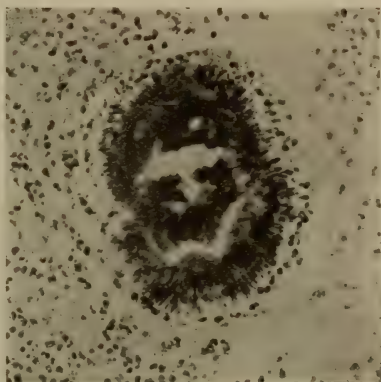


FIG. 32.—ACTINOMYCES CLUSTER SHOWING RADIAL STRIATIONS AT PERIPHERY (Karg and Schmorl).

## MYCETOMA

*Mycetoma* or *Madura foot* is a chronic specific inflammatory condition caused by the *Actinomyces maduræ*. This organism closely resembles the *A. bovis*, but the club-shaped extremities are absent and spores may occur along the threads. Can be grown artificially; stains by the ordinary methods and by Gram's.

Usually attacks but one foot, particularly the great toe, but may involve the leg, arm, or hand. A nodule slowly appears,



FIG. 33.—ACTINOMYCES OF MADURA FOOT (Wright and Brown). Granule crushed beneath a cover-glass, showing radial striations in the hyaline masses. Preparation not stained; low magnifying power.

and in the course of a year or two may soften and discharge a thin pus in which are found minute rounded bodies resembling fish-roe. These bodies may be either pinkish in color, the *pale* or *ochroid* variety, or black like gunpowder, the *melanoid* form.

On account of the degeneration numerous sinuses may form. The disease is painless and seldom fatal.

## SYPHILIS

Is a specific, infectious, and very contagious disease of man. By experimental inoculation it has been transmitted to the higher apes and rabbits.

Is due to the *Treponema pallidum* (*Spirochæta pallida*), an organism that has been so constantly found in syphilitic lesions that it seems most probable that it is the causative factor. This organism is long, actively motile, spiral or corkscrew in shape, and with pointed ends. It is from 4 to 20  $\mu$  long, 0.25  $\mu$  thick, and contains six to fourteen turns which are short, clear cut and regular. It is difficult to stain and to grow, but it has been obtained in pure culture.

The disease may be divided into the—

1. Period of primary incubation, about three weeks.
2. Period of primary symptoms, chancre and adenitis.
3. Period of secondary incubation, about six weeks.
4. Period of secondary symptoms, from one to three years.
5. Intermediate period of two to four years, during which the patient may recover.
6. Period of tertiary symptoms, unlimited.

The **primary lesion** is the *chancre*, which starts as a single papule, seldom multiple, at the seat of inoculation, which may be either *genital* or *extragenital*, and is invariably present except in congenital syphilis. This soon becomes eroded as a result of superficial necrosis, but increases in size due to infiltration of the deeper tissues. Is circular or oval, 1 by 1.5 cm., base hard. The edges are sharply defined, the induration not extending much beyond the lesion, and terminating abruptly. The chancre is slightly elevated and movable, not being adherent to the underlying tissues. Secretion is thin and scanty, suppuration being unusual; the surface may be dry or covered by a slight false membrane.

Microscopically there is a tremendous infiltration of cells, particularly in the neighborhood of the vessels, and marked changes in the walls of the blood-vessels. The infiltration begins with an escape of small round lymphoid cells, and this is accompanied by a proliferation of the cells of the cutaneous connective tissue and the cells of the walls of the blood-vessels. The elastic

tissue disappears, the new formation of cells extending along the small arteries and veins. The tissue becomes crowded with vari-

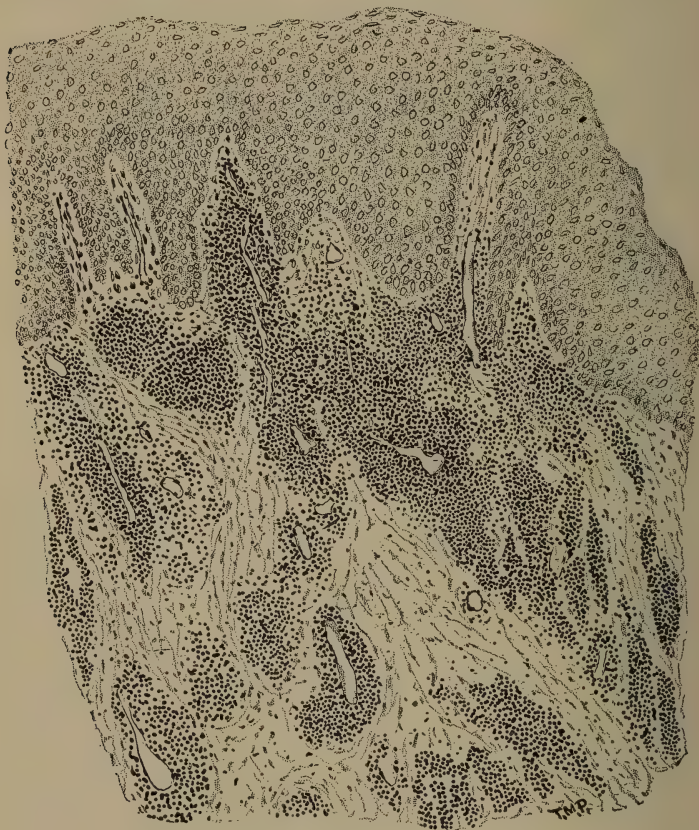


FIG. 34.—SECTION FROM A PRIMARY SYPHILITIC NODULE OF THE MUCOUS MEMBRANE OF THE MOUTH, SHOWING COLLECTIONS OF CELLS ABOUT THE BLOOD-VESSELS IN THE SUBMUCOUS TISSUE (Delafield and Prudden).

ous kinds of cells—polymorphonuclear leukocytes, lymphocytes, plasma cells, endothelial and connective-tissue cells, and fibroblasts. The media of the vessels thickens, the endothelium of

the intima proliferates, and the lumen may be partially or completely obstructed. As a result of the interference with the circulation degeneration begins. The vessels not infrequently show hyaline changes.

**Secondary Lesions.**—From the time the chancre begins to form the spread of the disease begins by invasion of the lymphatics. By the time the chancre is well developed enlargement of the neighboring lymph-nodes can be observed. This continues even after the chancre has disappeared, and the enlarged nodes are found to be hard, free from inflammation, painless, and movable. They also do not suppurate. The nodes most commonly involved are the postcervical, sternomastoid, submaxillary, epitrochlear, axillary, and inguinal. Enlargement of the epitrochlear is particularly suspicious, as it is seldom attacked except in syphilis.



FIG. 35.—UPPER MEDIAN INCISORS IN HEREDITARY SYPHILIS (Cornil and Ranvier).



FIG. 36.—SERRATIONS IN NORMAL TEETH (Cornil and Ranvier).

There then appear skin eruptions, polymorphic in character, accompanied by fever, constitutional symptoms, and a rapid decrease in the erythrocytes, with a moderate leukocytosis, usually of the lymphocytes. The skin lesions are generally symmetric, do not itch, and are coppery in appearance. May be some loss of hair, due to inflammation of the hair-follicles. The patches are irregular and have a “moth-eaten” appearance.

The *mucous patch* or *condyloma latum* appears on the mucous membrane and the contiguous skin surfaces, particularly those that are naturally warm and moist. It is a slightly elevated, moist, grayish lesion, covered by a thin pseudomembrane. In these there is round-cell infiltration of the skin, with superficial necrosis and edema. There may be one or more patches.

Although the chancre and the secondary lesions are highly contagious, the mucous patch is probably the most so.

The chief **tertiary** lesion is the *gumma*. It is found most commonly in the nose and nasal septum, scalp, iris, shoulders,

arms, and internal organs. The gumma develops as a nodular mass composed of great numbers of embryonic connective tissue and lymphoid cells with a very small amount of trabeculæ. Blood-vessels, most of them showing thickening of their walls, are numerous and may be found even during necrotic changes of the tissues. This would indicate that the breaking down processes are probably due largely to the syphilitic poison and not to obstruction of the vessels. It usually undergoes a caseous or other form of degeneration, with ulceration or absorption and subsequent cicatrization. It is hard, dense, and elastic.

When the growth of the gumma ceases, the younger peripheral cells become organized into connective-tissue cells, forming an envelope for the cheesy and gummatous center. This envelope shrinks, the semifluid portions are absorbed, and finally a scar, possibly calcareous, is left.

The blood-vessels show an endarteritis which closes or narrows the lumen. The remains of broken-down cells and particles of fat are present, and giant cells may be found. As the *Treponema pallida* have been found in gummata, and inoculations into apes have caused syphilis, the tertiary lesions must be considered infectious.

**Congenital syphilis** may result from disease of the ovum, spermatozoön, or both, or it may be transmitted through the placenta after conception has taken place, this being the most probable.

The mother, although showing no signs of syphilis, cannot be infected by nursing her child that is suffering from the disease (Colles' law).

Whether this immunity is real or whether the mother acquires it by being herself affected, although so lightly as to cause none of the usual symptoms, is still an unsettled question. As the Wassermann reaction is generally positive with the mother's serum, it would seem that she is usually infected.

An apparently healthy baby born of a syphilitic mother cannot be infected by her (Profeta's law). This apparent immunity may indicate that the child has received a true but latent infection, one that may not make its appearance until later in life.

The fetus may die *in utero* and be aborted, the child may be born dead, or it may be alive, but die shortly after birth.

The primary lesion does not occur in the hereditary form, but the secondary and tertiary manifestations may be evident, such as skin eruptions and mucous patches or even gummata. The characteristic lesion of congenital syphilis is pemphigus. There are present on the palms or the soles blister-like elevations of the skin containing a bloody or a greenish fluid.

The upper incisors of the second dentition are frequently conical and peg shaped, with deep notches at the free edge (Hutchinson's teeth).

There also frequently occurs a "white" pneumonia, cirrhosis of the liver, spleen, and pancreas, osteochondritis, and interstitial keratitis.

## CHAPTER VIII

### PROGRESSIVE TISSUE CHANGES

#### HYPERTROPHY

HYPERTROPHY, generally speaking, means an enlargement or overgrowth of any kind. It is usually divided into *true* and *false* hypertrophy, or *hyperplasia*, as the latter is called.

**True hypertrophy** is a uniform enlargement of a part, dependent upon an increase in size of all of its component elements. Accompanying the enlargement there is an increase in the functional power of the part involved.

The hypertrophy may be either *congenital* or *acquired*. It may also be either *physiologic* or *pathologic*. The former, however, may come under the latter heading when it reaches a degree that is not normal to the individual.

Hypertrophy is called *compensatory* when one organ takes upon itself the amount of work that was primarily carried on by two; is known as *vicarious* when another function increases at the expense of one that has been destroyed.

*Etiology*.—1. *Congenital causes*, in which case there are marked overgrowths of portions of the body, especially of the fingers and toes.

2. *Exercise* calls for an increased amount of energy. This demand is met by a greater supply of food with a subsequent increase in size, and is seen in the enlarged muscles of a blacksmith, or in a kidney when the other one is diseased or absent. This latter is an example of *compensatory* hypertrophy.

3. *Nervous influences* in some indefinite way play a part in hypertrophy, as is seen in the enlargement and increased function of the mammary glands during pregnancy.

4. *Disease of the hypophysis cerebri* apparently causes the condition called *acromegaly*, in which the tissues of the face and extremities hypertrophy.

*Morbid Anatomy.*—The part affected is uniformly increased in size.

Microscopically hypertrophy may be divided into the *simple* or *true* and the *numeric* (hyperplasia).

In the *simple* there is an increase in the size of the individual cell. This is seen particularly in the pregnant uterus, where at term the unstriped muscle cells may be eleven times as long and four times as broad as normal.

In the *numeric* variety the cells increase in number, but not necessarily in size; may even be smaller than normal.

**Hyperplasia, or false hypertrophy**, is a condition in which there is an increase in number of the cells with usually an asymmetric enlargement of the tissue. It is an excess of one constituent of an organ without a corresponding growth of the other elements.

The fibrous connective tissue is most commonly involved.

*Etiology.*—1. *Irritation* is the most common cause, if not too severe in character. In that case inflammation with consequent degeneration results.

The irritation may be *mechanical*, such as results from intermittent pressure exerted by tight shoes, or from the presence of a foreign body. *Chemical* irritants, such as alcohol, will bring about an increase in the amount of connective tissue, particularly in the liver, in which case there is also an increase in the number of bile capillaries.

2. *Nervous influences*, such as bring about the condition known as pseudohypertrophic muscular paralysis. In it there is not an increase in the muscle itself, but the fat has undergone a hyperplasia. There is also a fatty degeneration, with atrophy of muscle-fibers.

3. *Compensatory*, such as occurs when, on account of the decrease in size of an organ, the surrounding tissues have undergone a hyperplasia in order to supply the deficiency.

*Morbid Anatomy.*—The part involved may be much larger than normal or, on account of the contraction of the newly formed connective tissue, be much smaller. In either case the change is not symmetric.

In elephantiasis the part involved will be irregularly enlarged

as a result of the obstruction of the lymphatics and the increase in the number of cells.

In hyperplasia of the connective tissue of the liver the organ may be smaller than normal and have a roughly granular surface.

*Metaplasia* refers to the transformation of one tissue into one of another variety. The new variety must, however, be one derived from the same blastodermic layer. There is not, however, a development of less specialized tissues into a higher type; a simple epithelium cannot, in the vertebrates, give rise to a more complex glandular tissue or to nerve-cells. Columnar epithelium may become converted into stratified squamous epithelium with keratosis, as in the uterus, gall-bladder, or larynx. This change is more common in the connective-tissue group, as in the formation of fat from areolar tissue, of bone from fibrous tissue, etc.

*Heteroplasia* is the development of a new tissue in a locality where it is not normally found. This is seen particularly in connection with neoplasms.

*Anaplasia* refers to the reversion of a cell to a less specialized stage. It is a change occurring preparatory to an increased proliferation. Is applied mainly to tumor formation. Hanse-mann's studies of tumor cells show that unequal, asymmetric and multipolar mitosis, and destruction of chromosomes is of frequent occurrence, especially in the more malignant tumors. The term "anaplasia" is applied to these cells, signifying a loss of normal differentiation, of specific function, and of organization.

Anaplastic cells are, therefore, not embryonal cells, but a new type which has lost its place in the old organization.

## CHAPTER IX

### TUMORS OR NEOPLASMS

A *tumor* is an abnormal mass of cells or tissues resembling those normally present, but arranged atypically. It grows without any definite limit at the expense of the organism, without serving any useful function.

The cause of such growths is as yet unknown. They are made up of tissues that have their counterpart either in the embryonal or adult development. They differ in having a more or less atypical arrangement, in occurring in tissues in which they are heterologous, and in not having any mechanism to control their growth and function. Inflammation is unessential to their occurrence, and their structure is dissimilar to that of inflammatory lesions. There is no hyperemia, no exudation, no leukocytic invasion, no granulation tissue, no cicatrization. Tumors tend to increase and persist, while most inflammations tend to recover and disappear. Inflammatory growths always consist of connective tissue, regardless of the tissue or organ in which they occur.

**Theories of Origin.**—They are numerous, but as yet no one answers in every case.

1. *Spermatic Influence.*—It was thought that the normal tissue where the growth occurred had become directly transformed into the tissue of the tumor, but this is not in any way supported.

2. *Mechanical Irritation Theory of Virchow.*—By this it is claimed that new growths arise in tissues that have been the seat of injury or chronic irritation. Such cases as the development of epitheliomata on the lower lips of pipe-smokers, carcinoma of the gall-bladder associated with gall-stones, scrotal cancer in chimney-sweeps, x-ray cancer, cancer of mouth in Ceylon, Kangri cancer in natives of Kashmir, etc., would seem

to uphold this theory. It is probable, however, that the injuries and irritation are not the causative, but are predisposing, factors.

3. *Theory of Embryonic Remnants* (Cohnheim).—The author of this theory believed that “in an early stage of embryonic development more cells were produced than were required for the formation of the tissue involved, so that there remained unused a number of cells, possibly very few, which, on account of their embryonic character, were endowed with the power of marked proliferation.” These remnants are frequently spoken of as “rests.” Cohnheim thought that they could lie latent for many years and develop in after-life if conditions should become favorable. No explanation is given, however, as to what is meant by “favorable conditions.”

Such groups of cells have been observed not infrequently in various tissues and organs of the body. Adrenal rests are not uncommon. In certain forms of tumors this theory seems to hold good: in enchondromata of the testis and parotid glands and of other organs, and particularly in the case of the dermoid cysts.

4. *Parasitic or Infective Theory*.—It has been claimed by many investigators, especially concerning the carcinomata and sarcomata, that tumors are caused by the presence of living micro-organisms. Bacteria were first supposed to be the cause, but protozoa and blastomycetes have also been suspected. The general opinion, however, is that these cell inclusions are portions of broken-down nuclei or else secretions of the cells. Attempts to grow these bodies have, as a rule, resulted in failures, or, if grown, have not reproduced the disease in other animals. Up to the present no specific micro-organism has been demonstrated in cancer or in any other spontaneous new growth. Attempts to transplant human carcinoma from one person to another have not as yet been successful, although transplants of tumors have been made in many generations of mice and rats. Success occurs only when the growth has been implanted in other animals of similar kind. Such experiments, nevertheless, do not show the necessity of any low form of organism. It is well known that portions of skin can be transplanted from

one person to another. More recently attempts have been successful in causing sarcoma-like tumors to grow in hens that have been inoculated with a filtered extract of the growth.

5. *Theory of Decreased Tissue Resistance*.—Ribbert's theory is that the connective tissue loses its normal resisting power or "tissue tension," and by doing so allows the epithelial cells to undergo abnormal proliferation. The essential feature is that the cells must become separated from their normal relation to the surrounding tissue and then take on an active growth.

This theory is not satisfactory, as in the healing of wounds scattered groups of epithelial cells are found constantly which have actively pushed over and into the underlying granulation tissue, yet tumor formation in such cases is exceptional.

6. *Nervous Theory*.—This was to the effect that through disturbances of the trophic nerves the tissues were able to undergo an overgrowth. Certain investigators have shown what seems to be a definite correspondence between the occurrence of skin cancer and the distribution of certain cutaneous nerves.

Of other theories, that of Adami is interesting. According to him the cell, instead of adhering to the habit of function, has reverted to an earlier stage, one in which the habit of growth predominates. The energy, therefore, that primarily was devoted to the performance of function is now directed to growth, and there is then formed a mass of uncontrolled cells. This view gains support in that many of the malignant tumors appear at a time when the function of the tissue is at a decline.

A general survey of the field would indicate that true tumors are not parasitic in nature. That the condition is one in which the potential activity of the cell is sufficient to give rise to unlimited growth if the restricting barrier, whatever that may be, be removed. To that extent the cancer cell itself may be considered in the light of a parasite. It has been shown that in the rat certain tissues ordinarily resistant to the implantation of bits of rat tumor may become susceptible as a result of some

pre-existing irritation, To this condition has been applied the term *precancerous stage*. In the human being there are certain lesions of the mammary gland that although in themselves non-cancerous may later become so.

**Predisposing Causes.**—*Age*.—Certain tumors apparently bear a distinct relationship to the age of the individual. Before thirty years the sarcomata are most likely to appear; after that period, the carcinomata.

*Sex*.—On account of the frequent involvement of the female genitalia women are much more commonly the victims of cancer than men.

*Heredity* may have some influence, as it has been found that carcinomata are more common in some families than in others.

*Occupation*, as in chimney-sweepers and in paraffin-workers, who seem to frequently suffer from carcinoma. Probably the result of chronic irritation due to a lack of cleanliness.

**Morphology.**—Tumors may differ greatly in the following respects:

*Size*.—They may be of any size, from microscopic to weighing 275 pounds, as reported by Delameter.

*Shape*.—According to their shape tumors are called *nodular* when spheric, *tubercles* when projecting as a rounded body above the surface of an organ, *flat* or *tabular* when rising as a comparatively level elevation.

When the growth is connected to its original site by a stalk or pedicle it is called a *polyp*. When the surface is very roughened and irregular the tumor may be termed a *cauliflower* or *dendritic* growth.

If like a mushroom with a narrow stalk and a broad head, it is termed a *fungus*.

*Color*.—The color of a growth depends upon the nature of the tissue of which it is composed, upon the amount of blood present, and the presence of pigment. It may also be modified if degenerative processes have taken place.

*Consistency* depends upon the structure of the growth and upon the presence or absence of degenerations. If of bone the tumor will be very hard; if of mucous tissue, very soft.

*Number.*—Tumors may be *single* or *multiple*, there being usually a single *primary* tumor with several *secondary* ones if the growth is malignant, these latter being of the same type as the primary. There may, however, be hundreds of primary tumors, as in cases of fibroma molluscum. Sometimes there may be several primary tumors of different histologic types.

A *recurrent* tumor is one that recurs at the place from which it was removed.

According to the arrangement, tumors may be *typical*, *hemoplastic*, or *homologous* when they resemble the tissue from which they arise; *atypical*, *heteroplastic*, or *heterologous* when they differ.

If made up of a simple tissue they are called *histoid* tumors; if of a combination, attempting the formation of an organ, *organoid*; and when containing portions of all three blastodermic layers, *teratoid*.

The blood-vessels, which always originate from pre-existing vessels, may be greatly increased in number, *telangiectatic*; in size, *cavernous*; or unusually arranged, *plexiform*. These may be greatly decreased in number, thereby favoring secondary changes, or their walls may be imperfectly formed, giving rise to hemorrhages. Capillaries are commonly absent. Lymphatics are usually present, but the nervous supply is very poor, as a rule.

The *growth* of a tumor is independent of that of the individual. It may continue even if the normal tissues are being sacrificed for it. A lipoma will grow although the patient may not be getting sufficient nourishment to carry on the normal functions of the body.

It may be either *central expansion*, as is the case in benign growths, or *peripheral infiltration*, as in the malignant forms. The latter also increase by means of the central expansion.

As the blood-supply of tumors is usually poor, they frequently undergo various forms of degeneration, as *pigmentation*, *calcification*, *fatty*, *hyaline*, *colloid*, and *muroid* metamorphoses; *necrosis* and *ulceration*.

According to their effect upon the individual a new growth may be either *benign* or *malignant*.

**Benign growths** do not affect the patient except as they may press upon vital structures or undergo degenerative processes.

They are usually circumscribed, encapsulated, do not give metastases, and do not recur after excision.

**Malignant tumors** are those that through their own influences tend to bring about the death of the individual. They are not circumscribed nor encapsulated, cause cachexia, probably toxic in origin, give metastasis, and recur after excision.

*Metastasis* refers to the extension of the primary growth by the transference of malignant cells to other parts of the body. In *carcinoma* this takes place, as a rule, by means of the lymphatics. As the original tumor increases in size its cells penetrate the surrounding tissues, and on account of the decreased resistance tend to grow along the lymphatic spaces. In this way distant growths may be directly connected with the primary focus by means of these strands. This is frequently spoken of as the *permeation* method. As the tumor extends, it is the neighboring lymph-nodes that first show secondary involvement. The extension continues until a chain of lymph-nodes is attacked. It is also very probable that extension by means of the blood may occur indirectly in carcinoma. The tumor cells may gain entrance to the thoracic duct and thus get into the circulation. They then usually lodge in the liver and give rise to new masses. Under other conditions, such as necrosis and ulceration, the cancer cells can enter directly into the blood.

In *sarcoma* extension takes place only by means of the blood, the walls of the vessels being very incomplete and easily allowing the entrance of tumor cells.

**Death** may be caused by tumors—

1. *Pressing* upon vital organs.
2. *Invading* vital organs and causing degeneration.
3. *Hemorrhage* resulting from ulceration and degeneration.
4. *Absorption* of poisonous products.
5. *Secondary infection*.
6. *Exhaustion* due to the tumor using up so much nutrition for its own benefit.

**Classification of Tumors.**—The simplest is as follows:

## I. HISTOID.

### *Simple Connective-tissue Tumors.*

	<i>Atypical.</i>	<i>Typical.</i>
<i>Embryonic type</i> .....	Sarcoma.	Connective tissue.
<i>Adult type</i> .....	Fibroma { Hard } { Soft }	Connective tissue.
	Lipoma.	Fatty tissue.
	Myxoma.	Mucous tissue.
	Chondroma.	Cartilage.
	Osteoma.	Bone.
	Glioma.	Neuroglia.

### *Specialized Connective-tissue Tumors.*

Myoma {	Rhabdo-.....	Striated muscle.
	Leio-.....	Non-striated muscle.
Hemangioma.....		Blood-vessels.
Lymphangioma.....		Lymph-vessels.
Lymphadenoma.....		Lymphatic tissue.
Lymphoma.....		Lymphatic tissue.

### *Type of Endothelium.*

Endothelioma.

## II. ORGANOID.—*Epithelial Tumors.*

Neuroma .....	Nerve tissue.
Squamous epithelioma .....	Squamous epithelium.
Hard papilloma .....	Squamous epithelium.
Soft papilloma .....	Columnar epithelium.
Cylindric epithelioma .....	Columnar epithelium.
Adenoma	} ..... Normal glandular type of cells.
Hypernephroma }	
Carcinoma.....	Atypical glandular cells.

## III. TERATOID.—*Mixed Tumors.*

Dermoids.  
Teratoma.  
Cholesteatoma.

## IV. CHORIO-EPITHELIOMA, SYNCYTIOMA MALIGNUM.—*Deciduoma Malignum.*

Combinations of tumors that have been derived from the same blastodermic layer frequently occur, as fibrosarcoma,

fibromyoma, etc. One type, however, cannot be transformed into another.

The following classification of Adami's is recommended as being the most logical on account of its having been based upon a careful study of the histogenesis of the tissues.

Adami explains the classification as follows: "We thus find that the embryo comes to exhibit cell collections of two orders, which may be termed 'lining membranes' and (for lack of a more expressive word) 'pulp,' the 'lining membranes' being the persistent epiblastic, hypoblastic, mesothelial, and endothelial layers, the 'pulp' being the main mass of the neuroblast (of epiblastic origin), the notochord (of hypoblastic), and the mesenchyme (of mesoblastic). And now, following up the development of these different cell collections, we observe that the adult tissues derived from these two series exhibit well-marked differences, so that we can divide adult tissues into two great groups—the *lepidic* (from λεπις, λεπιδος, a rind, skin, or membrane) and the *hylic* (ὕλη, crude undifferentiated material).

"The characteristic of the lepidic tissues is that the specific cells which give them their main features are arranged either in layers or clusters *in direct apposition; they are not separated by lymph-spaces or by blood-vessels*; they possess, nevertheless, a supporting framework or stroma of hylic tissue in which run the nutrient vessels. Of the hylic tissues, the features are the opposite: *separating the cells there is a matrix of intracellular substance*, either homogeneous or fibrillated, while *lymph-spaces and blood capillaries tend to separate and run between the individual cells*.

"If in the lepidic tissues there is a stroma of hylic tissues, so here in the hylic there always enters lepidic tissue in the shape of the living endothelium of the blood- and lymph-vessels. In either case the elements of the other order occupy a subordinate position. While some pathologists, like O. Israel and Buxton, have already noticed this distinction, the histologists and embryologists have laid little stress upon it. The more we study tumors, the more we realize the importance of the distinction."

On this basis we obtain the following classification of normal tissues:

## I. LEPIDIC, OR LINING MEMBRANE TISSUES,

*in which the blood-vessels do not penetrate the groups of specific cells and in which there is an absence of definite stroma between the individual cells, although such stroma, of mesenchymatous origin, may be present between the groups of cells.*

## 1. Epiblastic:

Epidermis. Epidermal appendages of the hair, nails, enamel of the teeth, etc. Epidermal glands. Epithelium of the mouth and salivary glands. Epithelium and glands of the nasal tract and associated spaces. Epidermal portion of the hypophysis cerebri. The lens of the eye. Epithelium of the membranous labyrinth of the ear, anus, and male urethra (except the prostatic portion).

## 2. Hypoblastic:

Epithelium of the digestive tract and glands connected with it. Specific cells of the liver, pancreas, tonsils, thymus, and thyroid. Epithelium of the trachea, lungs, bladder, female urethra, and male urethra (prostatic portion).

## 3. Mesothelial:

Lining cells of the pleuræ, pericardium, peritoneum. Specific cells of the suprarenals, kidneys, testes, and ovaries (Graafian follicles). Epithelium and glands of the Fallopian tubes, uterus, vagina, vasa deferentia, vesiculæ seminales, etc.

## 4. Endothelial:

Lining endothelium of the blood-vessels and lymphatics.

## II. HYLIC, OR PRIMITIVE PULP TISSUES.

*Organs and tissues in which the special characteristic is that the specific cells lie in, and are separated by, a definite stroma, homogeneous or fibrillar, in which there may or may not be blood and lymph-vessels.*

## 1. Epiblastic:

Nerve-cells; neuroglia.

## 2. Hypoblastic:

Notochord.

## 3. Mesenchymatous:

Fibrous connective tissues, cartilage, bone, reticulum of lymph-glands, bone-marrow, fat-cells, involuntary muscle tissue, spleen, blood-vessels, blood-corpuscles.

## 4. Mesothelial:

Striated muscle, including cardiac muscle.

“Following this scheme of classification of the normal tissues, we may now divide the tumors arising from the specific constituent cells of the various tissues into two main genera—the *lepidic* tumors or *lepidomata*, originating from the above ‘lining membrane’ tissues and the *hylic* tumors (*hylomata*), originating from tissues derived from the embryonic ‘pulp.’ We can further distinguish two broad groups of lepidic tumors—the *primary*, those whose cells are derived in direct descent from the original epiblast and hypoblast, and the *secondary*, or *transitional*, whose

cells are derived in indirect descent from the same—*i. e.*, have in the course of development passed through a mesoblastic or mesenchymatous stage before coming to form portions of a lining membrane.”

In the classification that follows the author has not followed the exact wording of Dr. Adami, but has introduced such modifications as shall be consistent with his own text:

## I. LEPIDIC, OR RIND TUMORS.

### A. LEPIDOMATA OF THE FIRST ORDER.

#### 1. *Of Epiblastic Origin.*

Tumors (epitheliomata) whose characteristic constituents are overgrowths of tissues derived directly from the epiblastic “lining membranes” or epiderm.

##### (a) *Typical.*—Papilloma.

Adenoma of the sweat-glands.

Adenoma of the sebaceous glands.

Adenoma of the mammary glands, etc.

##### (b) *Atypical.*—Squamous-cell carcinoma.

Carcinoma of glands of epiblastic origin.

#### 2. *Of Hypoblastic Origin.*

##### (a) *Typical.*—Papilloma of the digestive and respiratory organs and bladder.

Adenoma of the digestive and respiratory tracts, thyroid, pancreas, liver, bladder, etc.

##### (b) *Atypical.*—Carcinoma developing in the same organs and regions.

### B. LEPIDOMATA OF THE SECOND ORDER OR TRANSITIONAL LEPIDOMATA.

#### 3. *Of Mesothelial Origin.*

Tumors (mesotheliomata) whose characteristic constituents are cells derived in direct descent from the persistent mesothelium of the embryo.

##### (a) *Typical.*—Adenoma of the kidney, testicle, ovary, urogenital ducts; uterus, prostate.

*Mesothelioma*—adenoma of the serous membranes of the pleura, peritoneum, etc.

##### (b) *Atypical.*—Cancer of the above-mentioned organs; squamous endothelioma, so-called, of serous surfaces, epithelioma of the vagina; adrenal mesotheliomata, hypernephroma.

#### 4. *Of Endothelial Origin.*

Tumors (endotheliomata) originating from the endothelium of the blood- and lymph-vessels:

Lymphangio-endothelioma.

Hemangio-endothelioma.

Perithelioma.

Cylindroma.

Psammoma.

Cholesteatoma.

## II. HYLIC, OR "PULP" TUMORS.

1. *Of Epiblastic Origin.*

Tumors whose characteristic constituents are overgrowths of tissues derived from the embryonic pulp of epiblastic origin.

(a) *Typical.*—Neuroma.

Glioma.

(b) *Atypical.*—Gliosarcoma.2. *Of Hypoblastic Origin.*

Tumors derived similarly from embryonic pulp of hypoblastic origin.  
Chordoma.

3. *Of Mesenchymal Origin.*

A. *Mesenchymal Hylomata.*—Derived from tissues originating from the persistent mesoblastic pulp or mesenchyme.

(a) *Typical.*—Fibroma.

Lipoma.

Chondroma.

Osteoma.

Myxoma.

Leiomyoma.

Angioma.

Myeloma.

Lymphoma.

(b) *Atypical.*—Derived from mesenchymatous tissues.

Sarcoma.—Fibrosarcoma.

Spindle-cell sarcoma.

Oat-cell-shaped sarcoma.

Chondrosarcoma.

Osteosarcoma.

Myxosarcoma.

Lymphosarcoma.

Chloroma.

Angiosarcoma.

Melanosarcoma (debatable).

B. *Mesothelial Hylomata.*—Tumors which are overgrowths similarly of tissues derived from embryonal pulp of definitely mesothelial origin.

Rhabdomyoma.

## TUMORS OF EMBRYONAL CONNECTIVE TISSUE

## SARCOMA

A *sarcoma* is a tumor made up of cells that resemble physically those found in embryonal connective tissues. As a rule the greater the departure from the adult cell, the greater is the malignancy. They are characterized by the preponderance of the cells over the intercellular substance, which may be granular, fibrillary, or reticular. The sarcoma cells are not truly embryonal, as they never continue to a complete development. They

arise from the mesoblastic layer and often retain the characteristics of the tissue from which they arise, periosteal sarcomata sometimes containing bone.

The sarcomata are essentially malignant; that is, they infiltrate the surrounding tissues, give metastases, cause cachexia, and return after excision. It is only occasionally that they are encapsulated.

The blood-vessels are generally few in number and imperfectly formed, the single layer of endothelium being supported by a very few connective-tissue fibers. In many cases the blood-channels are simply spaces whose walls are formed by the tumor cells. The imperfect vessel wall explains why hemorrhage in these tumors is so common and why *metastasis* takes place by means of the blood.

Sometimes the blood-spaces may be very large and numerous, thus forming the angiosarcoma.

As a rule, no lymphatics are present.

Sarcomata may occur in any part of the body; as a rule, they are seldom primary within organs.

They generally occur before the age of thirty. Are frequently rounded in shape, somewhat lobulated, and to a certain degree circumscribed. Are hard or soft according to the amount of intercellular substance present, or to the variety of the tissue of which they are composed.

Their color is generally pink or grayish; this, however, depends to a great extent upon the condition and number of the blood-vessels.

On account of the poor blood-supply, degenerations, particularly *myxomatous*, frequently take place. Interstitial hemorrhages as a result of the degeneration are not infrequent.

If there is pigment present, either melanin or hemosiderin, the tumor is called a *pigmented* one.

These tumors vary greatly in their malignancy, the small round-cell type, especially if melanotic, being rapidly fatal. The greater the amount of cellular elements, the greater is the malignancy.

The **varieties** of the tumors depend upon the kind of cell that predominates.

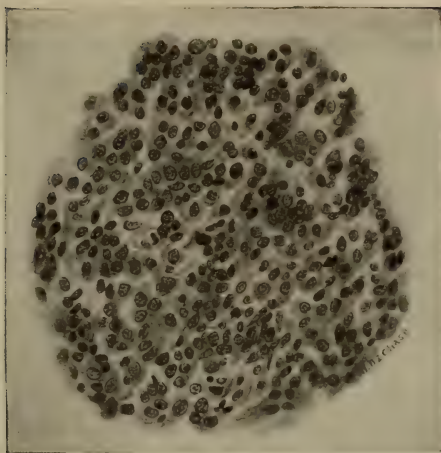


FIG. 37.—SMALL ROUND-CELL SARCOMA OF THE LOWER JAW. Oc. 3; ob. D. D. (McFarland).

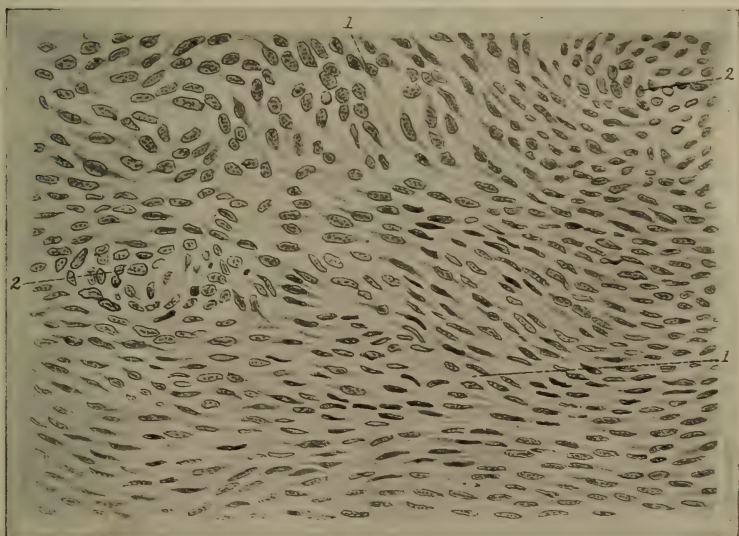


FIG. 38.—SPINDLE-CELL SARCOMA FROM THE BRAIN.  $\times 300$  (Dürck).  
1, Spindle cells cut longitudinally; 2, spindle cells in transverse section.

*Round-cell sarcomata* are those made up of either *large* or *small* round cells.

In the *small-cell* variety the intercellular substance is very scanty. They are rather soft, whitish in color, friable, and a milky juice can be scraped from the cut surface.

They grow rapidly, infiltrate the surrounding tissues, give extensive metastasis, recur quickly after removal, and soon



FIG. 39.—GIANT-CELL SARCOMA OF THE THIGH (McFarland).

*a*, Giant cells; *b*, spindle cells.

cause death. They may occur in any part of the body and at any age.

The individual cells have large vesicular nuclei, that stain deeply, and comparatively little protoplasm.

If there is a close resemblance to the arrangement of a lymph-node, small round cells with a distinct reticulum, the tumor is called a *lymphosarcoma*.

The *large round-cell sarcoma* is very similar to the small, but is firmer on account of the intercellular connective tissue present. The cells are larger, and although generally round, may be polygonal, and are sometimes arranged in alveoli.

Are less malignant than the small.

*Spindle-cell sarcoma* is one that is made up of spindle cells, either large or small. Is one of the commonest forms.

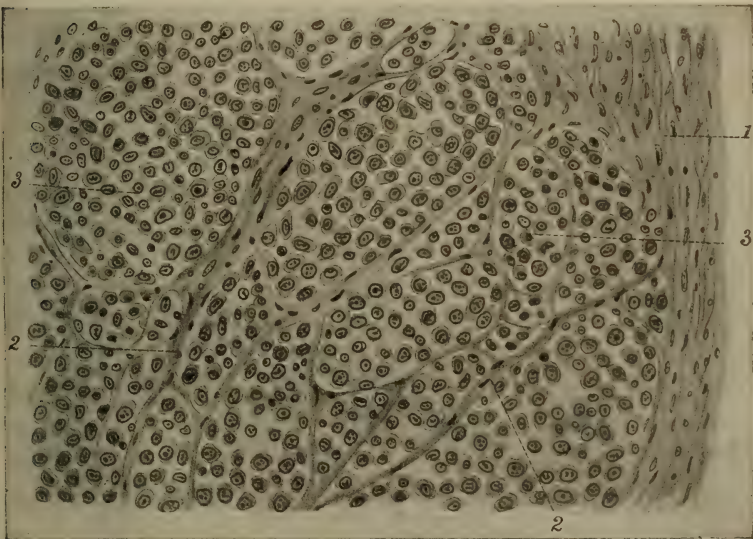


FIG. 40.—ALVEOLAR LARGE ROUND-CELLED SARCOMA FROM THE PERIOSTEUM.  $\times 250$  (Dürck).

1, Heavy septum of connective tissue; 2, delicate connective-tissue reticulum; 3, polyhedral cells with vesicular nuclei.

These tumors are quite firm, white, and very little juice can be scraped from the cut surface. The cells are arranged in irregular bundles and have oval vesicular nuclei. The amount of intercellular tissue may be very great, making the tumor quite hard; is then known as a *fibrosarcoma* and is but slightly malignant. It is often difficult to determine whether the tumor is a sarcoma or a fibroma.

The spindle-cell sarcomata are relatively benign; they frequently do not give metastasis, although recurring after removal.

*Giant-cell sarcoma* is one in which there are found cells made up of a large amount of cytoplasm in which are numerous oval nuclei centrally located. The predominating cells may be round or spindle shaped. They are most commonly found in relation with bone and periosteum. When occurring on the jaw are

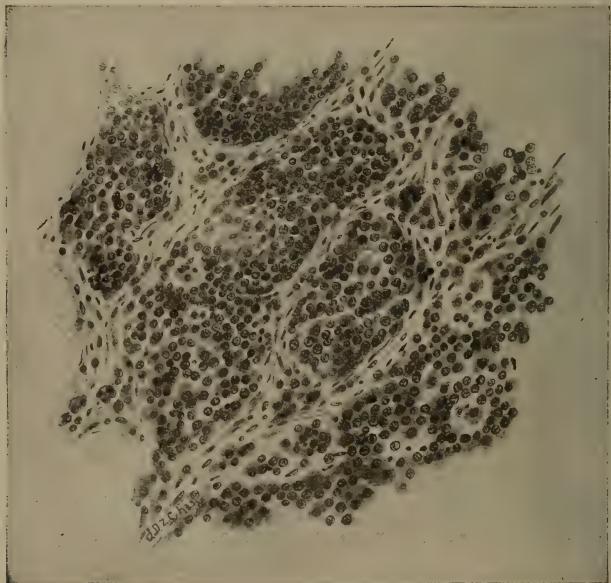


FIG. 41.—ALVEOLAR SMALL ROUND-CELL SARCOMA. Zeiss, Oc. 4; ob. c. (McFarland).

sometimes referred to as *epulis*, although the same term may be applied to a simple fibrous tumor.

This form is the least malignant of all the sarcomata.

*Special* names have been given to other forms of sarcoma on account of some special feature.

*Alveolar sarcoma* is where either groups of round or spindle cells are surrounded by distinct bands of connective tissue. This form may very closely resemble carcinoma.

*Melanotic sarcoma* is one of any type in which there is *melanin* present. This pigment may be found either in the cells or in the intercellular tissue.

They occur in the skin, the choroid coat of the eye, and in the ciliary body.

Are very malignant, give widespread metastasis, and rapidly prove fatal. The liver is the common secondary seat, particularly after primary melanotic sarcoma of the eye.

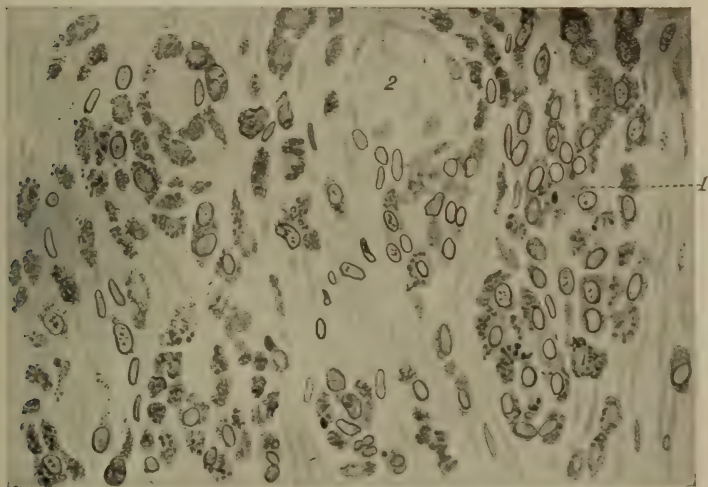


FIG. 42.—METASTATIC MELANOSARCOMA OF THE PERITONEUM.  $\times 320$  (Dürck).

1, Nests of darkly pigmented polygonal cells; 2, cross-section of vessels.

*Myxosarcoma* is one in which there is a marked mucoid degeneration present.

*Angiosarcoma* is a growth that contains many blood-vessels. If the walls of these vessels or the neighboring cells undergo a hyaline degeneration, the sarcoma is spoken of as a *cylindroma*.

If the tissue with the exception of those cells in the immediate neighborhood of the vessels undergoes a mucoid change, the growth is called a *myxangiosarcoma tubulare*.

*Chloroma* is a variety of sarcoma arising from the periosteum of the skull; is greenish in color. It may be that this form is more closely related to the tumor formations occurring in leukemia.

*Psammoma* is a tumor allied to the sarcoma. It is made up of masses of spindle cells, which contain areas of hyaline



FIG. 43.—PERITHELIOMA OF THE RETINA (McFarland).

*a*, Blood-vessels surrounded by cells in a good state of preservation; *b*, degenerated portion of tumor.

degeneration and calcification. Are usually found in the meninges of the brain and spinal cord.

*Endothelioma* is a tumor arising from endothelial cells. These growths are at times very difficult to differentiate from carcinoma on account of the apparent cell nest arrangement, but careful examination will commonly show some sarcomatous areas.

The cells extend along the lymphatic spaces and are closely related to connective tissue. Are found in the serous membranes, testicle, ovary, liver, and parotid. Are malignant.

Under this same heading are included those tumors developing from the cells in the lymph-spaces, the *lymphangio-endothelioma*; and those from the endothelium of the blood-vessels, the *heman-*



FIG. 44.—ENDOTHELIOMA OF THE PLEURA. Zeiss, Oc. 2; ob. c. (McFarland). The illustration shows the cellular growth in the form of cylindric masses which fill crevices of the tissue, probably originally channels.

*gio-endothelioma*. Occasionally some of these tumors arise from the perivascular endothelium, and to these has been given the name *perithelioma*. The cells in these latter are arranged in strands radiating from the vessel around which the mass originated.

According to the combination of tissues present sarcomata

may be further classified as follows; all such varieties, however, not being mentioned:

Osteosarcoma	=	bone present.
Chondrosarcoma	=	cartilage present.
Myosarcoma	=	muscle present.
Neurosarcoma	=	nerves present.

### TUMORS OF ADULT CONNECTIVE TISSUE

**Fibroma** is a tumor of fibrous connective tissue. Fibromata are usually pale in color, round, lobulated, circumscribed, and encapsulated. They may be of varying degrees of firmness.

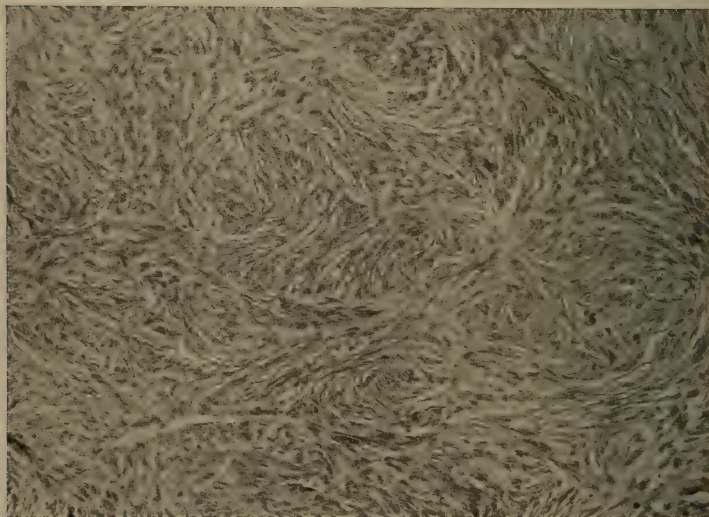


FIG. 45.—FIBROMA. CELLS AND FIBRILS IN SMALL BUNDLES WHICH RUN IN EVERY DIRECTION (Mallory).

The cells resemble those of normal connective tissue and are arranged in bundles that cross each other in all directions.

In the *soft* variety the cells are separated by serous or mucous deposits.

In the *hard* variety the cells are closely packed together.

Fibromata are benign and frequently undergo various degenerations. Occur in all parts of the body, particularly in the uterus, where they attain great size. In this locality are usually combined with muscle tissue, forming the *fibromyomata*.

They may occur in combination with sarcoma, or any of the various forms of adult connective tissue, as fibrolipoma, myxoma, chondroma, etc.

A *keloid* is a fibrous tumor that forms usually from a scar. It is not confined to the seat of the original injury, but extends somewhat into the surrounding tissues. Is usually smooth, and is most frequently seen in negroes.

*Molluscum fibrosum* is a condition in which there is a non-inflammatory overgrowth of the fibrous structures of the nerves, particularly those of the skin and subcutaneous tissues. Such tumors may occur singly or be present by the thousand over all parts of the body.

*Epulis* is a fibrous growth originating from the gum, usually at the site of diseased teeth.

**Myxoma** is a benign tumor made up of mucous tissue. Is usually pale in color, round, lobulated, encapsulated, and feels semifluid. On section a thick, viscid fluid exudes.

Microscopically spindle and stellate cells with long processes that anastomose are seen. In the meshes between the cells and processes is the mucous material. This substance is precipitated by acetic acid.

They occur in sheaths of tendons and nerves and in nasal and pharyngeal polyps, and in combination with sarcoma. Muroid growths forming from degeneration of fibromata are not true examples of myxomata.

**Lipoma** is a benign tumor made up of fatty tissue. Is yellow in color, round, lobulated, encapsulated, and soft. May be very large. Microscopically the cells resemble ordinary fatty tissue, except in being considerably larger and the connective-tissue trabeculae are also thicker than normal. Occurs most commonly in the subcutaneous tissue, in fasciae, and in synovial membranes. Is slow in growth and will frequently persist even if the individual is much emaciated. The blood-supply

is poor, and such tumors may undergo various forms of infiltration and degeneration, as calcification, ossification, necrosis, etc.

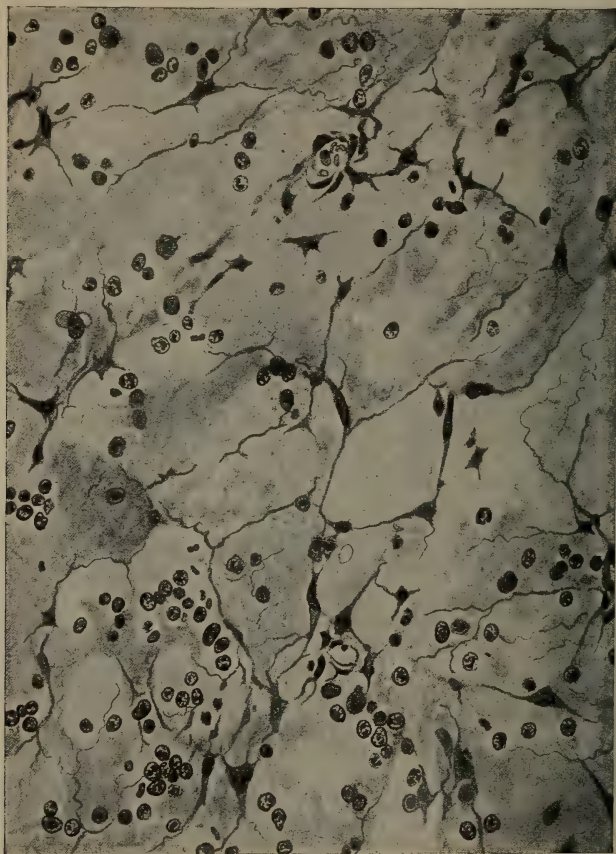


FIG. 46.—MYXOMATOUS FIBROMA OF THE NASAL MUCOUS MEMBRANE (Dürk).

Stellate connective-tissue cells joined together with protoplasmic processes; the intercellular substance has become myxomatous and contains abundant masses of leukocytes.

Occurs in combination with sarcoma, myxoma, fibroma, and angioma.

**Chondroma** is a growth composed of either hyaline or fibrous cartilage.

Arises from pre-existing cartilages, periosteum, or the medullary substance of the long bones. If it is found in localities where periosteum does not exist, as in the testicles and lungs, is called an *enchondroma*.

Is hard, encapsulated, and lobulated. Is slow in growth, may persist for years, and become very large.

Frequently undergoes mucoid degeneration and calcareous infiltration.

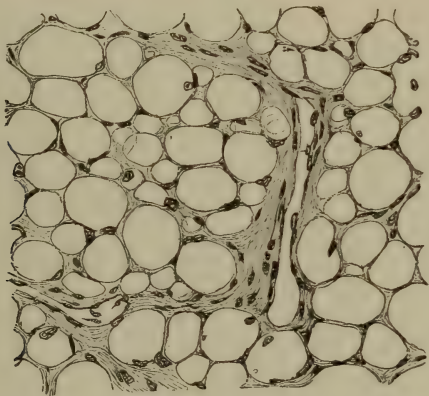


FIG. 47.—LIPOMA FROM THE REGION OF THE SHOULDER WITH RELATIVELY SMALL FAT CELLS. (M. Fl. Häm.)  $\times 300$  (Ziegler).

Is benign, but in combination with sarcoma may be quite malignant. Is also found in combination with lipoma, fibroma, and myxoma. An *ecchondroma* is a small overgrowth of cartilage. Are found on the edges of the articular, laryngeal, and nasal cartilages.

**Osteoma** is a tumor composed of bone. It may be a result of inflammatory processes of the periosteum or be a distinct new growth.

If developing from a bone-forming tissue, is called an *homologous* osteoma.

If arising in a tissue that is not bone forming, is called a

*heterologous* osteoma. The latter are found in the meninges, lung, and parotid gland.

An osteoma is a hard, bony, rounded, and more or less lobulated growth. Microscopically it presents quite typically the normal structure of bone. May be composed of spongy or compact new bone, osteoma spongiosum and osteoma durum.



FIG. 48.—HYALINE CHONDROMA. Oc. 2; ob. 3 (McFarland).

If the growth is small, circumscribed and flat, and arising from pre-existing bone, it is called an *osteophyte*. If irregular and projecting, an *exostosis*.

Occurs most commonly at the epiphyses of long bones. Is benign. May be in combination with cartilage, fibrous tissue, fat, or sarcoma, in which latter case it is malignant.

**Myoma** is a tumor composed of newly formed muscle-fibers. According as to whether the muscle is striped and voluntary, or unstriped and involuntary, we have the *rhabdomyoma* and the *leiomyoma*.

The first is very uncommon, but occurs in the kidney, heart, and uterus.

The latter occur frequently in the uterus and broad ligament, but may arise wherever there is involuntary muscle.

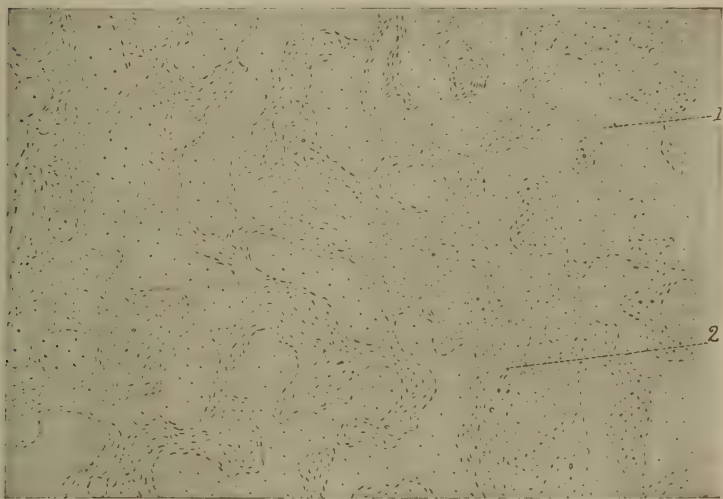


FIG. 49.—OSTEOMA OF THE LUNG.  $\times 75$  (Dürck).

1, Bone-trabeculae; 2, fibrous interspaces not presenting the characters of medullary spaces.

May be single or multiple. Are firm, round, lobulated growths, dark reddish in color. Microscopically they consist of elongated spindle cells, with rod-shaped nuclei collected in bundles that interlace in all directions.

Are benign, slow of growth, and frequently undergo cystic or calcareous degeneration. The cysts contain mucus.

Usually are in combination with fibroma.

**Neuroma** is a tumor composed of nerve tissue. As the

term has been applied to all growths found on nerves, two divisions are made: the *true* neuroma, which consists of nerve tissue; and the *false* neuroma, which consists of fibroconnective tissue.

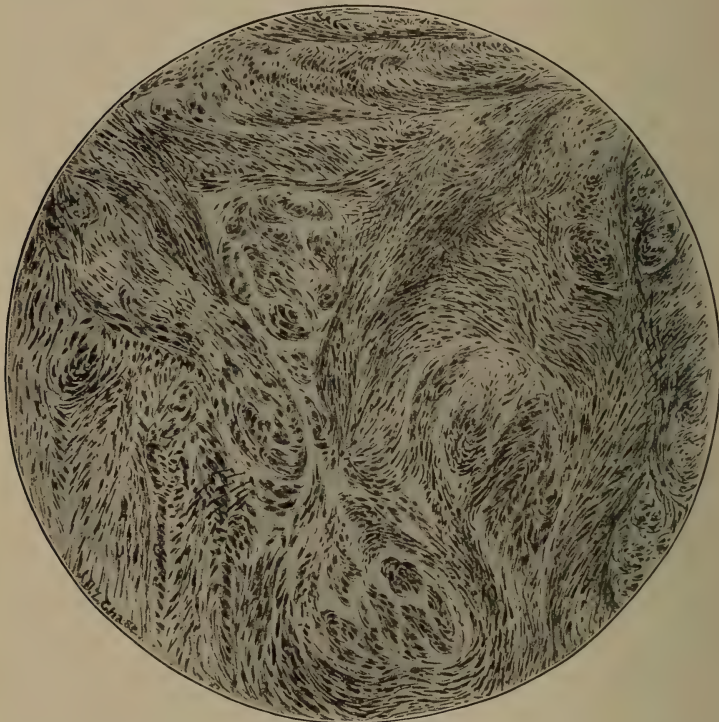


FIG. 50.—LEIOMYOMA OF THE UTERUS (UTERINE FIBROID). Oc. 4; ob. 3 (McFarland).

The true is called a *ganglionic* neuroma when ganglionic nerve-cells are present; if nerve-fibers only are present, it is called a *fibrillar* neuroma.

**Hemangioma** is a tumor made up of blood-vessels separated by a small amount of connective tissue.

*Angioma simplex* or *nevus* when the vessels are small and

very much interwoven. To this class belong the reddish discolorations known as birth-marks.

*Cavernous angioma* when the blood-spaces are large and separated by distinct fibrous bands. Resembles the structure of the corpus cavernosum of the penis.

*Plexiform angioma* when a group of more or less parallel blood-vessels become tortuous and widely dilated.

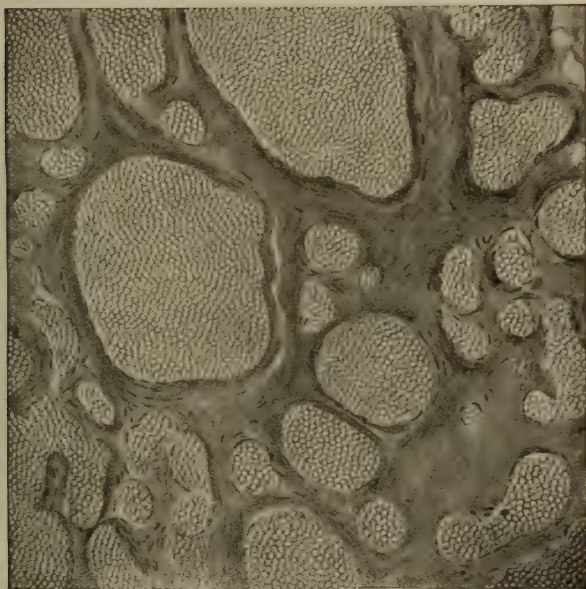


FIG. 51.—CAVERNOUS ANGIOMA (Warren).

**Lymphangioma** is a tumor caused by a dilatation of lymphatic vessels with an arrangement quite similar to that of the hemangioma.

An **odontoma**, according to Bland-Sutton, from whose work the following is taken, is a tumor composed of dental tissues in varying proportions and different degrees of development, arising from the teeth germs, or teeth still in the process of growth.

The species of this genus are determined according to the part of the tooth germ concerned in their formation.

- |                                  |                              |
|----------------------------------|------------------------------|
| 1. Epithelial odontoma           | = from the enamel organ.     |
| 2. Follicular odontoma,          | } = from the tooth follicle. |
| 3. Fibrous odontoma,             |                              |
| 4. Cementoma,                    |                              |
| 5. Compound follicular odontoma, |                              |
| 6. Radicular odontoma            | = from the papilla.          |
| 7. Composite odontoma            | = from the whole germ.       |

1. *Epithelial odontoma* occur, as a rule, in the mandible, but they have been observed in the maxilla. They have a fairly



FIG. 52.—EPITHELIAL ODONTOMA. NATURAL SIZE (Bland-Sutton).

firm capsule, and in section display a collection of cysts of various shapes and sizes, but the openings rarely exceed 2 cm. in diameter. The cysts are separated by thin fibrous septa, sometimes ossified. The cavities contain a brown mucoid fluid which gives a reddish tint to the growing portions of the tumor. Histologically, an epithelial odontoma consists of branching and anastomosing columns of epithelium, portions of which form alveoli. The cells occupying the alveoli vary, the outer layer may be columnar, while the central cells degenerate and give rise to tissue resembling the stellate reticulum of an enamel organ. It may be that many of these tumors do not arise from the epithelial enamel organ, but from endothelium within the gums.

Figures 52 to 61 inclusive are from "Tumours, Innocent and Malignant," by Sir John Bland-Sutton, F. R. C. S.

2. *Follicular odontoma* comprise those swellings often called "dentigerous cysts," an inaccurate term. They arise commonly

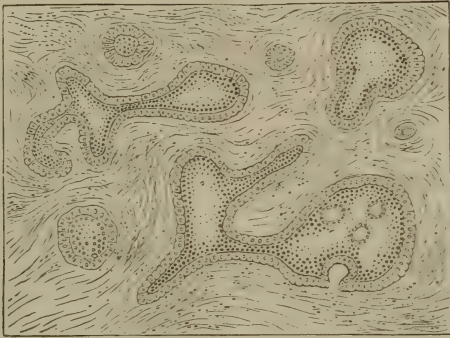


FIG. 53.—MICROSCOPIC CHARACTERS OF AN EPITHELIAL ODONTOMA (Bland-Sutton).

in connection with teeth of the permanent set, and especially with the molars. Sometimes they attain large dimensions and



FIG. 54.—A FOLLICULAR ODONTOMA FROM THE RIGHT HALF OF THE MANDIBLE OF A BOY AGED FOURTEEN YEARS.

Removed by Wormald, 1850 (Museum Royal College of Surgeons).

produce great deformities, particularly when they arise in the upper jaws and happen to be bilateral. Occasionally they occur in connection with supernumerary teeth. The tumor

consists of a wall of varying thickness, which represents an expanded tooth follicle; in some cases it is thin and crepitant, in others it may be as much as 1 cm. thick. The cavity of the cyst usually contains viscid fluid and the crown or the roof of an

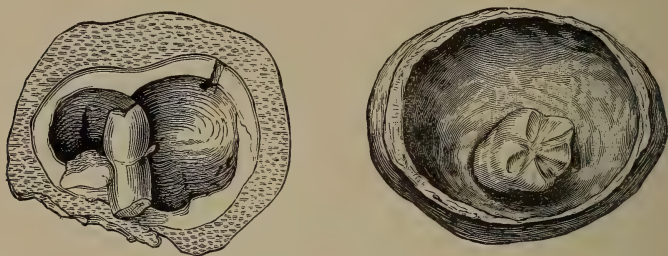


FIG. 55.—FOLLICULAR ODONTOMATA FROM THE MANDIBLE (Bland-Sutton).

imperfectly developed tooth. Occasionally the tooth is loose in the follicle, sometimes inverted, and often its root is truncated. Exceptionally the tooth is absent, or is represented by an ill-shaped denticle. The walls of the cyst always contain



FIG. 56.—AN ODONTOMA FROM THE MANDIBLE OF A RICKETY YOUTH AGED NINETEEN YEARS.

A, Denticle; B, portion of the outer wall of the jaw (Bland-Sutton).

lime or osseous matter, the amount varying considerably. These tumors are not unknown in other animals, having been found in sheep, pigs, and porcupines. The amount of fluid in a follicular odontoma varies, and the size of the tumor depends in the main upon this. Sometimes the fluid may measure

as much as 2 ounces, and this may lead to the wide separation of the inner and outer plates of the body of the mandible, and the odontoma may occupy the entire length of the bone.



FIG. 57.—ODONTOMA SURROUNDING THE SECOND MANDIBULAR MOLAR OF A BOY AGED FIFTEEN YEARS (Bland-Sutton).



FIG. 58.—THE ODONTOMA IN SECTION, SHOWING THE RELATION OF THE ROOTS TO THE TUMOR TISSUE (Bland-Sutton).



FIG. 59.—FIBROUS ODONTOMA FROM A GOAT. NATURAL SIZE (Bland-Sutton).

3. *Fibrous Odontoma*.—In a developing tooth, a portion of the connective tissue in which it is embedded is found to be

denser and more vascular than the rest; it also presents a fibrillar arrangement. This condensed tissue is known as the tooth sac, and, when fully developed, presents an outer firm wall and an inner looser layer of tissue. At the root of the tooth the follicle wall blends with the dentin papilla, and is indistinguishable from it. Before the tooth cuts the gum it is completely enclosed within this capsule. Under certain conditions this capsule becomes greatly increased in thickness and so thoroughly encysts the tooth that it is never erupted. Such thickened cap-

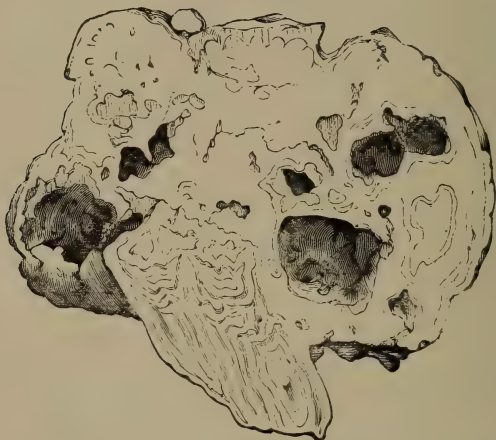


FIG. 60.—CEMENTOMA FROM A HORSE. HALF NATURAL SIZE (Museum Royal College of Surgeons).

sules are mistaken for fibrous tumors, especially if the tooth be small and ill developed. Under the microscope they present a laminated appearance, with strata of calcareous matter. To these the term "fibrous odontomata" may be applied. As a rule they are multiple, four being by no means an unusual number. There is good reason to believe that rickets is responsible for some of these thickened capsules.

4. *Cementoma*.—When the capsule of a tooth becomes enlarged, and these thick capsules ossify, the tooth will become embedded in a mass of cementum. To this form of odontoma

the name "cementoma" may be applied. Tumors of this character occur most frequently in horses. The chief structural peculiarity is the presence, in enormous numbers, of large, richly branched openings.

5. *Compound Follicular Odontoma*.—If the thickened capsule ossifies sporadically instead of uniformly, a curious condition is brought about, for the tumor will then contain a number of small fragments of cementum, or dentin, or even ill-shaped teeth (denticles) composed of three dental elements—cementum, dentin, and enamel. The number of teeth or denticles varies greatly, and may reach a total of four hundred.

6. *Radicular odontoma* is the term applied to those tumors which arise after the crown of the tooth has been completed, and while the roots are in the process of formation. As the crown of the tooth, when once formed, is unalterable, it naturally follows that should the root develop an odontoma, enamel cannot enter its composition; the tumor would consist of dentin and cementum in varying proportions, these two tissues being the result of the activity of the papilla. The outer layer of the odontoma is composed of cementum; within this is a layer of dentin, and inside this is a nucleus of calcified pulp. It is probable that some radicular odontomata in man are due to inflammatory changes.

7. *Composite odontoma* is a convenient term to apply to those hard tooth tumors which bear little or no resemblance in shape to teeth, but occur in the jaws, and consist of a disordered conglomeration of enamel, dentin, and cementum. Such odontoma may be considered as arising from an abnormal growth of all the elements of a tooth germ, enamel organ, papilla, and follicle. Not only is this growth composite in that the tumor originates from all the elements of a tooth germ, but it is composite in another sense: many of these tumors are composed of two or more tooth germs indiscriminately fused. But they differ from the cementomata containing two or more teeth in the fact that the various parts of the teeth composing the mass are indistinguishably mixed, whereas the individual teeth implicated in a cementoma can be clearly defined. It was long believed that composite odontomata occurred only in the mandible, but

it is clear not only that they arise as frequently in the maxillæ, but that they attain a far larger size in the upper than in the lower jaw.



FIG. 61.—COMPOSITE ODONTOMA. NATURAL SIZE (After Forget).

**Dental Cysts.**—It occasionally happens that in extracting permanent teeth a small fibrous bag is found at the apex of the root, often no larger than an apple seed, though sometimes it may be as large as a bantam's egg, filled with fluid, and often containing crystals of cholesterin. These sacs, or dental cysts, occur in connection with the dead roots of mandibular and maxillary teeth, especially molars and premolars. They sometimes attain a considerable size in the upper jaw when they invade the antrum, and some of these cysts are sufficiently large to simulate an abscess of that cavity. Dental cysts are often bilateral and occasionally multiple. The constant association of these cysts with the dead roots of permanent teeth has led many observers to regard them as pus-sacs with thick fibrous walls. Others, having demonstrated the existence of an epithelial lining in many of these cysts, believe that they arise in embryonal "rests," known as "paradental epithelial remnants."

## TUMORS OF EPITHELIAL TISSUES

A **papilloma** is a benign tumor composed of projections of fibrous connective tissue that are covered by one or more layers of epithelium, either squamous or columnar in type.

May be divided into the *hard* and the *soft* papilloma.



FIG. 62.—TUFT OF PAPILLOMA OF THE BLADDER (Stengel).

The *hard* occur on the skin as warts, and when so situated are commonly pigmented; also around the genitalia as a result of constant irritation, in which situation they are known as “venereal warts.” Are also found on the true vocal cords in the larynx. Are covered by squamous epithelium which commonly undergoes keratosis, a horny change. In this form the “pearly bodies” or “epithelial pearls” are frequently found. These are made up of cells concentrically arranged, many of

which have lost their nuclei and have become transformed into keratin. They are found only in squamous epithelium.

Papilloma covered by squamous epithelium are frequently found in the urinary bladder, and, although histologically benign, they very frequently undergo malignant changes.

The *soft* papilloma occur in the intestine, and are covered by columnar epithelium. This form quite frequently undergoes malignant transformation.

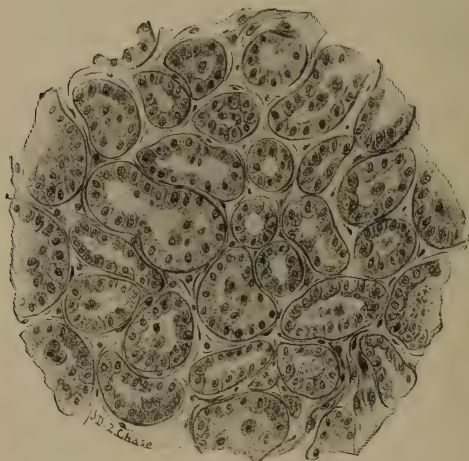


FIG. 63.—ALVEOLAR ADENOMA OF THE MAMMARY GLAND. Oc. 2; ob. 9 (McFarland).

The connective-tissue stalks may be simple projections or very complicated, branching outgrowths. They contain blood-vessels and lymphatics.

An **adenoma** is a tumor that in its structure resembles an epithelial gland. It is frequently very difficult to tell whether it is a true growth or only an enlargement of a normal gland.

In the new growth the tissues, though arranged typically, do not carry on any useful function. The secretion may be imperfect or there may be no duct through which it can escape.

Adenoma arise from epithelial glands, are circumscribed,

encapsulated and rounded, or nodular. Have been found in all glandular tissues.

Microscopically they consist of a framework of connective tissue, the meshes of which are covered by one or two layers of epithelial cells that resemble in shape and size those of the normal glands. The important point that distinguishes these growths from malignant ones is the relation of the cells to the



FIG. 64.—FIBRO-ADENOMA OF THE MAMMARY GLAND (CANALICULAR FORM).  
Oc. 2; ob. 3 (McFarland).

basement membrane. In the benign adenoma the membrane is preserved and the cells show no tendency to invade the surrounding tissue.

If the connective tissue and epithelium are in normal proportion the growth is called a *simple adenoma*; if the connective tissue predominates, a *fibro-adenoma*.

If the tumor has a pedicle, it is known as an *adenomatous polyp*.

Through degenerations, particularly colloid or mucoid, an adenoma may become very large through cystic formation. It is then called an *adenocystoma*.

If villi extend into the acini in the above form the growth is called an *adenocystoma papilliferum*.

**Hypernephroma** are tumors that resemble the cortical portion of the adrenal gland. They probably arise from misplaced portions of adrenal tissue, and, as such "rests" consist

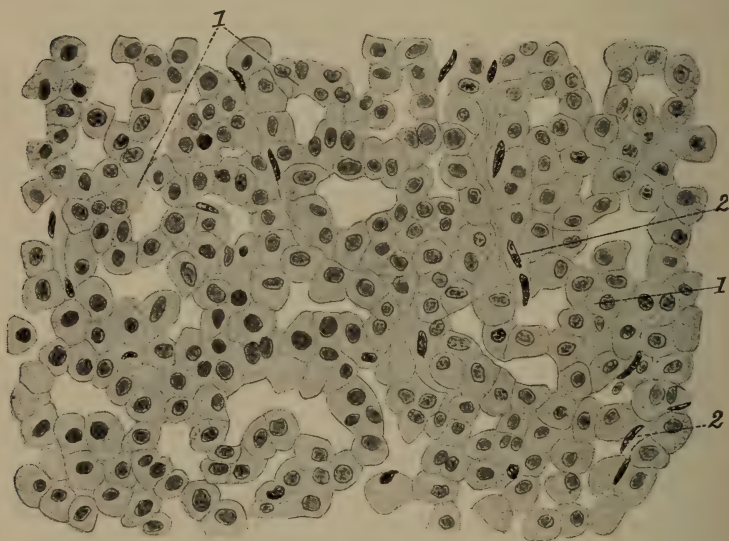


FIG. 65.—ADRENAL TUMOR FROM THE KIDNEY (HYPERNEPHROMA) (Dürck).

1, Large polygonal cells, containing an abundance of fat and arranged in tubes; 2, connective-tissue cells in the scanty stroma.

of only cortical elements, these tumors do not resemble the medulla of the gland nor do they contain epinephrin. Are found most commonly in the upper pole of the kidney, liver, broad ligament, and in other abdominal tissues.

Although commonly benign and encapsulated, they may take on a malignant change, infiltrate, and give rise to metastases by means of the blood-vessels.

The cells are large and vesicular, with large round, centrally placed nuclei. The connective-tissue framework is very slight. Dilated capillaries and areas of hemorrhage are common.

**Glioma** are growths composed of neuroglia or nervous connective tissue. As they arise from the epiblast, they cannot be classified with the mesoblastic tumors.

Are usually small, reddish in color, and not distinctly limited from surrounding tissues.

Microscopically they are composed of cells with large nuclei and with long fine processes.

Blood-vessels may be numerous and many areas of hemorrhage present.

Are benign and slow growing.

## CARCINOMA

A **carcinoma** is a malignant tumor of epithelial origin. It is characterized by a marked proliferation of epithelium with infiltration into the surrounding tissues.

The epithelium is arranged atypically in a supporting framework made up of adult connective tissue

The epithelial cells are not characteristic of the growth, but they differ in some respects from the normal type. The diagnosis of carcinoma cannot be made from the cell, as there is no distinct cancer cell. The general arrangement of epithelium and connective tissue must be taken into consideration.

The carcinomatous epithelium frequently consists of cells many times larger than normal. Their nuclei may be unusually large, vesicular, and show a peculiar affinity for nuclear stains, a condition called *hyperchromatosis*.

They may divide by an atypical mitosis and give rise to peculiar arrangements of the chromatin. These cells multiply rapidly, and, though at first round, they may become almost any shape on account of the mutual pressure exerted.

In some cases giant cells occur. Tumors of this variety differ greatly in size, shape, color, and density.

Carcinoma are composed of two types of tissue, epithelial and connective, cells and stroma. According to the one that predominates, carcinoma are called *medullary* when the cells are more numerous; *scirrhous* when the tumor is rich in connective tissue.

The first is soft; the second, hard.

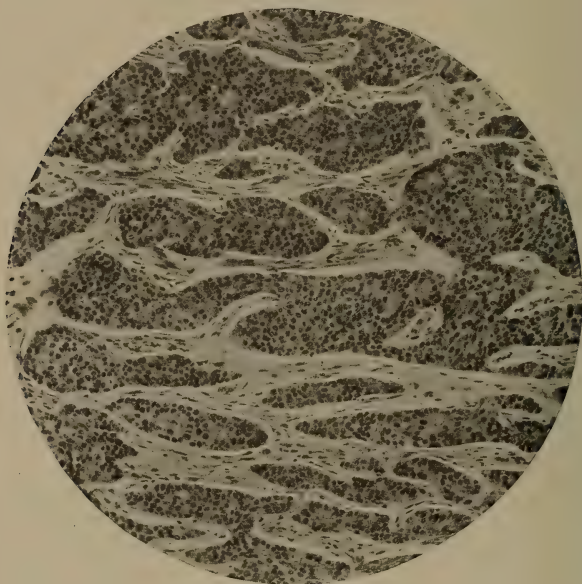


FIG. 66.—CARCINOMA OF MAMMARY GLAND (Mallory).  
Medullary type of growth. Slight tendency to the formation of gland lumina.

Well-developed blood-vessels and lymphatics are found in the stroma, which is most likely derived chiefly from pre-existing connective tissue, but a certain amount is probably newly formed. Elastic fibers are present in the infiltrating portion of the growth, but they are fragments of fibers pre-existing in the invaded tissue. The cellular elements originate from the epithelium normal to the part involved, and frequently retain the characteristics of the primary cell.

The more closely connected it is with the original cell, the more does the carcinoma cell resemble it. The further away it is, the greater is the variation. There is then a tendency to revert to the round, undifferentiated, embryonal type. Between the cells no fibrillary substance is found.

In carcinoma the cells frequently undergo degeneration, and usually of a form peculiar to the parent tissue. If it

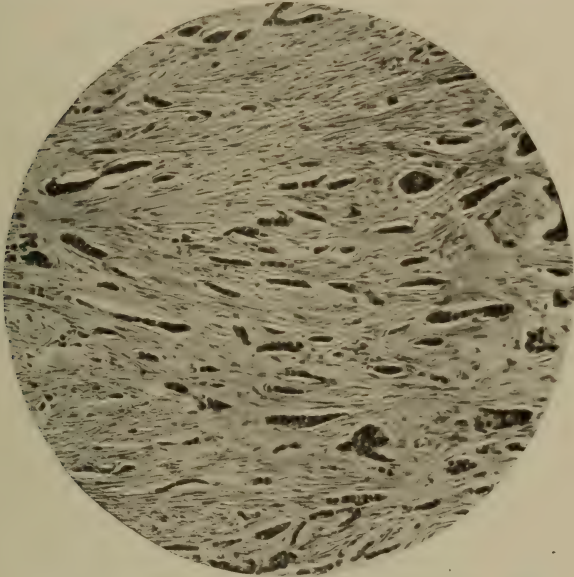


FIG. 67.—SCIRRHOUS CARCINOMA OF BREAST (Mallory).  
Alveoli of epithelial cells small; stroma abundant.

arose from squamous epithelium, keratin is found; colloid or mucoid material if derived from mucous membranes. The tumor may break down and undergo a fatty change, most common in the mammary gland.

A carcinoma may become infected and show marked inflammatory changes which may be so great as to somewhat disguise the true character of the growth. There will be an infiltration of the tissues with leukocytes.

Microscopically a carcinoma consists of columns of cells running in all directions, separated from one another by fibrous tissues. These columns give the appearance of alveoli filled with epithelium. The columns are branched into numerous subdivisions, giving a complicated root-like structure.

As the tumor grows these cells infiltrate and ramify in all directions, occupying usually the lymphatic spaces. Along

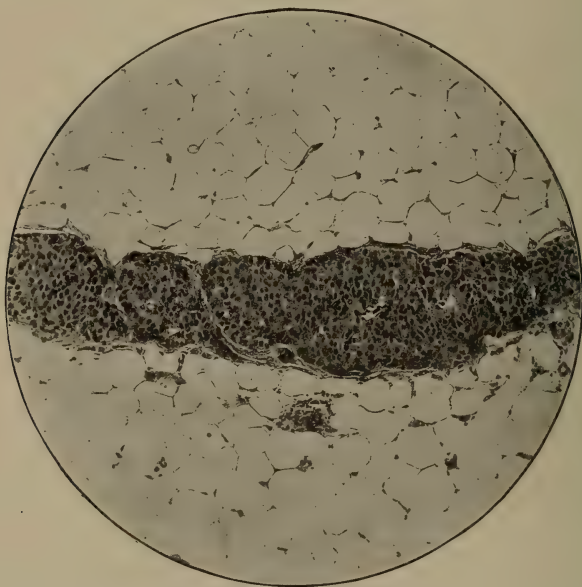


FIG. 68.—CARCINOMA OF MAMMARY GLAND (Mallory and Wolbach).  
Extension of tumor through a lymphatic in fat tissue.

the advancing border there is a more or less well-marked zone of round-cell infiltration.

As there is no intracellular substance, the cells easily break away from the main mass and are carried to the neighboring lymph-nodes. This may take place very early and give rise to extensive metastasis. These secondary growths are usually similar in character to the primary.

Extension to distant tissues may be due to *permeation*. According to this theory there is a continuous growth of cancer cells along the lymphatics of the deeper fascia, with widespread involvement.

A **squamous epithelioma** is a carcinoma that has arisen from a surface covered by stratified epithelium such as skin

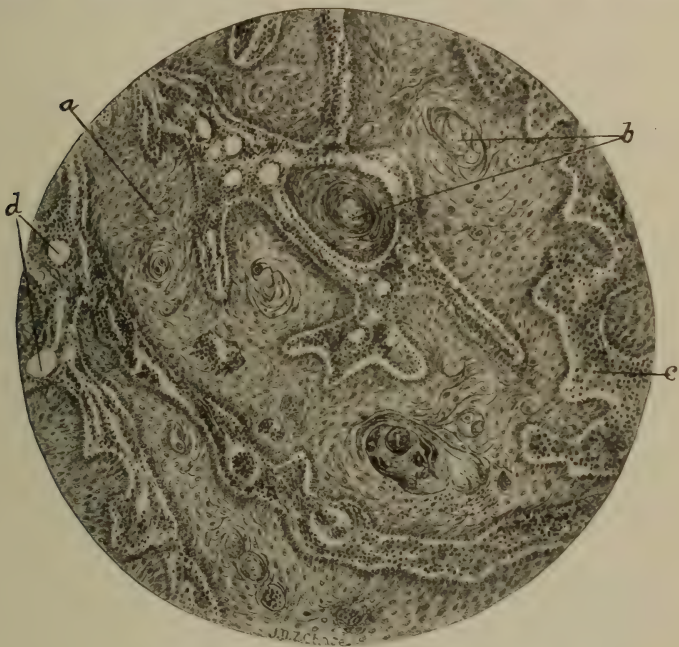


FIG. 69.—SQUAMOUS EPITHELIOMA (McFarland).

*a*, Epithelial masses; *b*, epithelial pearls; *c*, connective tissue; *d*, capillary blood-vessels.

and certain mucous membranes. It occurs most commonly on the cervix, the skin of the face, penis, vagina, and esophagus, especially wherever there is a junction of skin and mucous surfaces.

It makes its appearance as an indurated mass in which ulceration takes place rapidly and exposes a circular surface

with raised, hard edges. Sometimes it looks at first like a small wart.

Columns of these cells penetrate the tissues and on account of pressure arrange themselves in successive layers, the inner ones being almost flat and cornified, forming the *epithelial pearls*. *Hyperkeratosis* is the term used to indicate the cornification.

The presence of these pearls does not indicate that the tumor is necessarily malignant; they mean that the growth was derived from squamous epithelium. They are also not always found in squamous epitheliomata. The growth may have been so rapid as not to have allowed cornification to take place. As the cells infiltrate the surrounding tissue, there is a well-marked border zone of round cell infiltration, and the elastic tissue, as a rule, shows various forms of degeneration.

The cells are usually quite large, and may show numerous "prickles."

This form of carcinoma differs greatly in its malignancy. Some may exist for several years without showing much tendency to spread, but may suddenly grow and cause extensive destruction of tissue, with subsequent death of the patient. They recur on removal, and give metastasis by the lymphatics.

**X-Ray Carcinoma.**—As a result of long-continued exposure to the *x*-ray, chronic dermatitis very commonly develops. The superficial cells become necrotic, but in addition there is an involvement of deeper structures. Necrotic foci occur in the corium, probably due to vascular disturbances, such as a narrowing of the lumen of the vessels due to a proliferation of the endothelium. These deeper lesions may remain quiescent, but eventually the epidermis undergoes a downward proliferation, invades these foci, takes on an infiltrating character, and may give rise to very extensive metastases. The fingers and hands are usually the site of the primary lesion or lesions. The histologic structure of these growths is that of the squamous epithelioma.

*Rodent ulcer* or *carcinoma basocellulare* arises from the basal cells of the epidermis, particularly from those cells in the hair-follicles. Are most common in the region of the eyes and nose, usually occurring in men.

For many years—from three to twelve or more—there may be present a smooth, rounded nodule about the size of a pea. This may then break down and form an ulcer with rounded, smooth, and firm pearly gray edges. The ulceration may extend widely, bringing about extreme destruction of all the invaded tissues. It very rarely undergoes cicatrization, and seldom if ever gives metastasis or involves lymph-nodes. The



FIG. 70.—RODENT ULCER (Mallory).

cell nests have a peculiar roset form, due to the short, blunt projections of cells at the periphery. The nuclei are, as a rule, long, narrow and spindle shaped, and do not stain deeply. At the periphery of the cell nests the nuclei are arranged somewhat radially.

It is usually single, but may be multiple and may continue for many years—three to twenty-four.

An **adenocarcinoma** is a cancer in which the glandular struc-

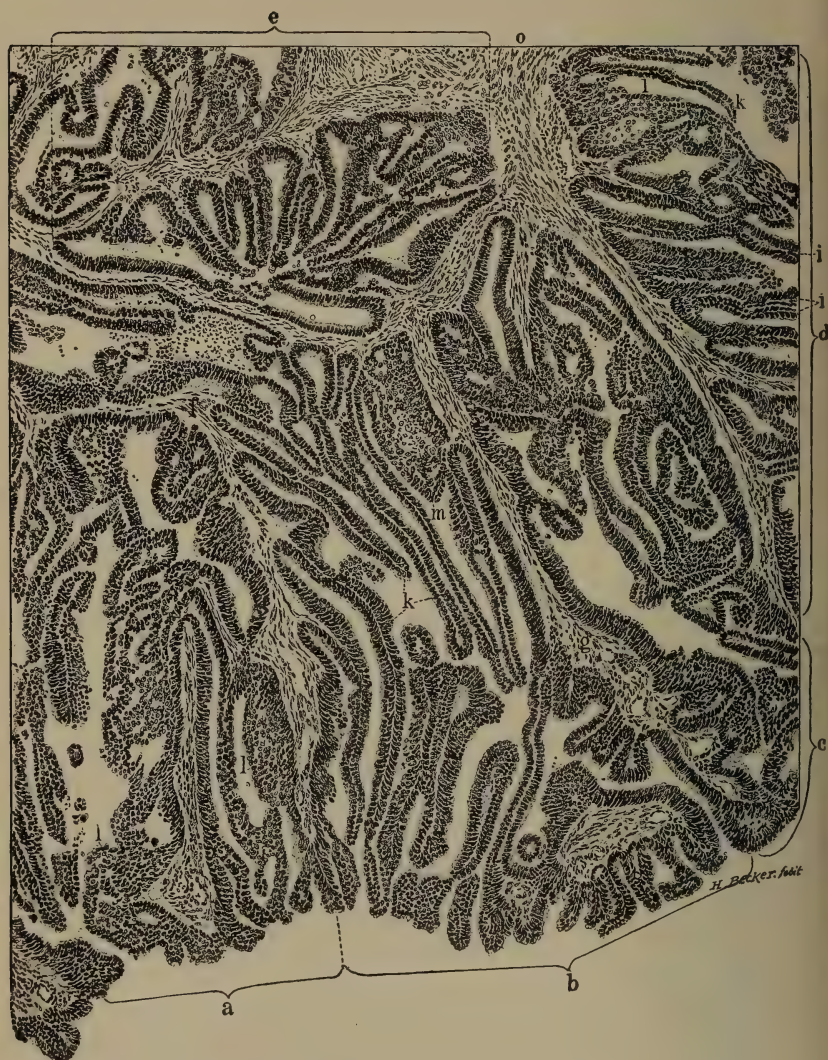


FIG. 71.—ADENOCARCINOMA OF THE BODY OF THE UTERUS (Cullen).

*o*, May be likened to a main stem from which arise numerous secondary stems, which in turn give off delicate terminals, consisting entirely of epi-

ture is to a great extent preserved, but the epithelium has taken on a proliferative growth. It either breaks through the basement membrane or else fills up the acini with numerous layers of cells. It is commonly found in the stomach, intestines, and uterus. Grows rapidly, gives metastasis, and quickly proves fatal.

The development of carcinoma differs greatly in different people. In some cases a continued mild irritation may precede. The growth may be very slow, but if for some reason there is an increase in the nutrition, as in the pregnant uterus, it may suddenly become rapid.

If the growth is rapid and metastasis extensive, the health of the patient suffers and cachexia develops. This may be the result of pain, of suppurative conditions, or from the absorption of toxic substances resulting from the disturbance of metabolism.

The etiology of carcinoma is still obscure. Heredity is apparently clear in many cases as a predisposing cause.

Age is of importance, the majority of cases appearing after thirty-five, a time when the resisting power of the tissues is beginning to diminish.

Carcinoma is more common in women than in men. In women it is in the genital organs; in men, in the intestinal tract.

Irritation and injury seem to at least be of some importance as exciting causes, although in themselves it is doubtful if they can give rise to a carcinoma.

Loss of resistance of the connective-tissue stroma has been advanced, but does not seem logical. Many observers have tried to prove that these growths are infectious processes, the results of parasitic activity. Many cellular inclusions resembling protozoa have been found, but the general opinion

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thelial cells. The glands may be divided into groups *a*, *b*, *c*, *d*, and *e*, by the stems of stroma *f*, *g*, and *h*. The stems are covered by several layers of cylindric epithelium, while projecting into the gland cavities are long slender ingrowths of epithelium, devoid of stroma, as seen in *i*. Very delicate ingrowths consisting merely of two layers of epithelium are seen at *k* and *k*. At *l* the epithelium is several layers in thickness, and at *m* many layers with leukocytes. The arborescent character of the growth and peculiar gland grouping are characteristic of adenocarcinoma.

at present is that these bodies are nothing more than degenerated cells or secretions of cells. Experiments to prove the infectious nature of carcinomata have not been generally successful. The transplantation of cancer tissue into a normal individual has failed. But when placed in another situation in the person from whom the tissue was excised growth has followed. This has frequently been considered proof of the parasitic nature. It probably means nothing more than

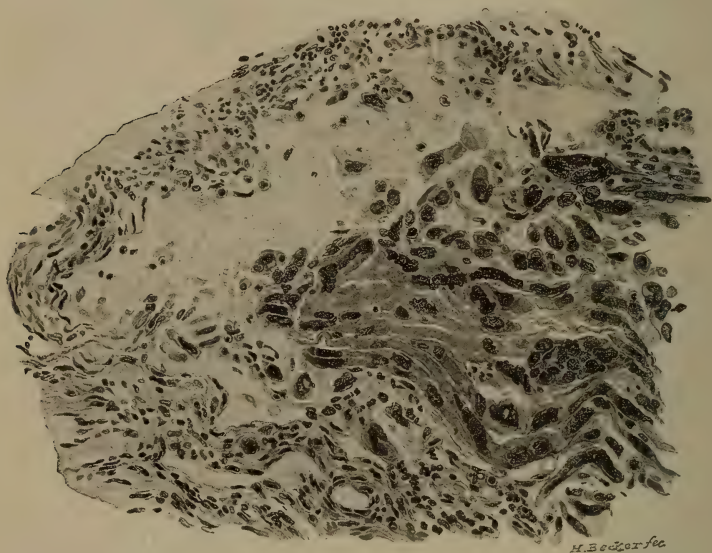


FIG. 72.—SYNCYTIAL MASSES INVADING A VENOUS CHANNEL IN A CASE OF DECIDUOMA MALIGNUM (J. Whitridge Williams).

that the pieces of tissue have found surroundings favoring their growth; a condition such as occurs in skin-grafting.

Bacteria, protozoa, sporozoa, gregarinæ, blastomycetes, amebæ, and fungi have all been suggested as the cause. These claims, however, rest upon the form of the bodies and their staining properties, not upon cultivation and inoculation. Until these latter can be carried out the parasite theory must remain unproved.

## CHORIO-EPITHELIOMA

The following discussion and classification is taken from Adami and McCrae:

To properly understand the formation of the chorio-epithelioma it will be necessary to review briefly the origin of the fetal placenta. This structure, arising from chorionic villi, finally develops a vascular mesoblastic core covered by epiblast. The outer cells of the fetal chorion erode into the mucous membranes of the uterus. Normally these cells, when they have penetrated into the sinuses, have done their work, and the outer layer becomes inactive, fuses, and forms the syncytium. Sometimes in cases of abortion these placental changes, usually complete by the time of full term, have not yet occurred, and when the immature fetus is expelled, there remain chorionic cells which have not degenerated and are still actively growing. These constitute the evil agent; they continue their growth in the uterus and form a neoplasm.

**Placental Mole.**—In some instances the fetus may die, be absorbed, and leave the placenta and membranes grafted upon the uterus in the form of an irregular fleshy mass, prone to hemorrhage and to putrefaction. On the other hand, the chorionic villi, being nourished by maternal blood, may grow actively and absorb fluid so that a villus becomes a vesicle or a series of vesicles. These may be large or small, due to distention by an edematous mucoid fluid. These vesicles may eventually take up as much room as a full-term fetus. Such an edematous mass of vesicles is known as a *hydatid mole*.

**Chorio-epithelioma.**—Such a hydatid mole as above described may pass beyond the usual growth and fill the uterine sinuses with polypoid masses, the so-called destructive placental polyp. The outer surface of the villus, consisting of fetal epiderm, becomes fused to form syncytium, which is made of deeply staining cells whose bodies have fused, the mass thus being multinuclear. Below the syncytial layer the cells of Langhans' layer remain unfused, individual, and less deeply staining. The syncytium possesses erosive and phagocytic properties, and it is these masses of cells that tend to be swept

away in the blood of the maternal sinuses and to be deposited in the capillaries of the lung and elsewhere.

**Chorio-epithelioma Malignum.**—This term is applied to a neoplasm that is entirely cellular, formed of large actively vegetative cells growing entirely within the vessels, not requiring an individual blood-supply by vessels of its own, not capsulated, liable to induce hemorrhage by erosion of the vessel walls, and very readily tending to have particles carried away to grow elsewhere. Such a tumor generally occurs shortly after an interrupted pregnancy, but may not occur for years after an abortion with no intervening pregnancy. Microscopically, various cells are seen. Very large ones containing many large nuclei, rich in chromatin, are formed by direct division. Others, much smaller, with single well-formed nuclei. Some that resemble lymphocytes, and all kinds of forms resembling the above types more or less closely. In places there may be found long narrow strands of protoplasm containing nuclei, but showing no division into individual cells, syncytium. Clinically, these tumors show great variations in malignancy, although microscopically their structure may be similar.

### TERATOMA

Under this heading are included those tumors which have a tendency to the formation not only of irregular cell masses, but also of fully formed organs, such as brain, teeth, skin, hair, bone, or secreting glands. Such growths may be due to the development of two germinal areas on one germinal vesicle, giving rise to double monsters, one of which undergoes inclusion in the other—*fetal inclusion*. They may result from the displacement of totipotent cells—those capable of giving origin to an individual—which become included in the growing organism. These cells may develop early and grow elaborately, giving rise to inclusions recognizable at birth. They may lie latent and at a subsequent time grow actively as abdominal inclusions, teratoma of the genital glands, and certain mixed tumors.

**Dermoid cysts, ovarian dermoids** are the most common of the teratoma. The cyst cavity is lined by squamous epi-

thelium in which are found sweat and sebaceous glands. Within the cavity is usually a varying amount of fatty material in which are masses of hair. In the wall of the cyst are found masses of bone to which teeth, usually but poorly formed, are attached. In some instances the extremities and genitalia have been seen.

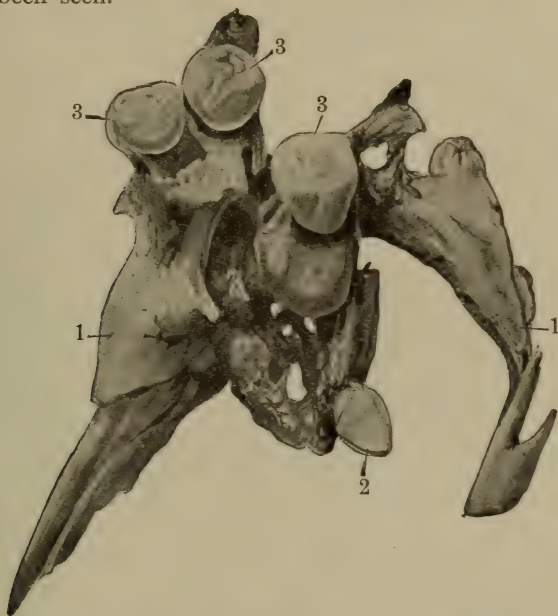


FIG. 73.—TEETH FROM OVARIAN DERMOID (From Coplin after Roberts).

An irregular branching piece of bone contained in a dermoid cyst of the ovary, in which are implanted well-formed teeth: 1, 1, Bony mass; 2, a tooth resembling a canine of the first dentition; 3, 3, 3, teeth resembling molars.

Somewhat similar growths may be found in those parts of the body where fetal clefts have united and in the median fissures of the body.

There is another type, the **sporadic teratoma**, which grow in regions bearing no relationship to the fissures, to the poles of the body, or to the generative glands, as in the anterior

mediastinum and the abdomen. These are probably due to the development of a misplaced totipotent cell. They generally consist of tissues from all three germinal layers. Sometimes the tissues are of adult appearance and of limited growth. More frequently they appear about puberty, grow rapidly, and tend to form secondary tumors.

### CYSTS

A *cyst* is a collection of a fluid or semifluid substance contained within a connective-tissue wall lined by epithelium or endothelium. The contained material may be serous, mucous, or purulent if infection has occurred.

Cysts may be either single or multilocular. The latter when divided into numerous compartments by fibrous partitions. These division walls may break down and convert a multilocular into a simple cyst.

Cysts may be divided into the following:

1. *Retention* cysts, resulting from an obstruction to the outflow of the secretion of a gland.
2. *Exudation* cysts, those formed by an increase of fluid in a closed cavity, as in the tunica vaginalis.
3. *Necrotic* or *liquefaction* cysts result from the breaking down of the central portion of solid tumors.
4. *Parasitic* cysts may occur on account of an inflammatory reaction around the parasite, or may be formed directly by it in its development.
5. *Dermoid* cysts belong to the teratomata, where they are described.
6. *Cystoma*, a cyst of neoplastic formation. They most frequently occur in the ovary and are multilocular.

## CHAPTER X

### SPECIAL PATHOLOGY OF THE MOUTH

**Malformations** of the lips and cheeks are usually associated with defective formation of the bones of the mouth. The entire process is usually due to an arrest of development or a failure of the branchial arches to fuse normally.

1. The lower jaw is absent; the upper jaw and hard palate are small and imperfectly formed; the temporal bones nearly touch in the median line. The lower part of the face, therefore, is lacking; the mouth is absent or small and closed posteriorly; the tongue is absent.

2. The face remains in its early fetal condition of a large cleft; the mouth and nose form one cavity; the orbits may be united in the same cavity.

3. There is a cleft in the upper lip, upper jaw, and hard palate. The cleft corresponds to the point of junction of the processes of the superior maxilla with the intermaxillary bone; consequently it occurs to one or the other side of the midline. There may be one cleft or two, one on either side of the intermaxillary bone. The cleft involves the lip alone—harelip—or the lip and superior maxilla, or the lip, maxilla, and palate. There may be a single or a double cleft in the palate, and the cleft may involve either the hard or soft palate or both. If there are two clefts of the lip and maxilla, the portion of lip and bone between them may be small or entirely absent, so as to leave a large open space. The soft palate may be absent entirely.

4. Rarely there is a cleft involving the middle of the lower lip and sometimes extending into the lower jaw.

5. Either the inferior or the superior or both maxillary bones may be abnormally small.

6. The edges of the lips may be partly or completely joined together. The opening of the mouth may be only a round hole.

7. The lips may be absent or imperfectly developed.

8. The corners of the mouth may be prolonged by clefts in the cheek reaching nearly to the ears.

**Anemia** of the mucous membranes of the mouth and lips is commonly seen in cases of general anemia, and is a well-recognized symptom.

**Hyperemia** of the active type is found in the various inflammations and as an early symptom in certain infectious diseases. Passive hyperemia occurs in the general congestion of chronic lung and heart disease. Actual bleeding is found in scurvy and purpura, and sometimes in the infectious fevers.

**Inflammation, Stomatitis.**—Inflammation of the mucous membranes of the mouth results from many causes, but particularly from local infection by bacteria.

*Catarrhal stomatitis* is most frequent in children, and may result from a great variety of local and general disturbances. The action of irritants, such as hot liquids, chemicals, decaying teeth, or from a depressed condition of the general system. The congestion and swelling of the mucous membrane may be well marked, and in chronic cases there is frequently a thickening of the mucous membrane with the formation of whitish areas. The mucous glands may enlarge and form small cysts. There is usually an increased amount of mucous secretion, but sometimes the membranes may be unnaturally dry. In addition to the hyperemia and local edema there may be proliferation, exfoliation, and degeneration of the epithelium. There may also be some infiltration of leukocytes.

*Ulcerative stomatitis* is usually found in children who are not well nourished. It occurs in malnutrition, tuberculosis, and in other chronic conditions, also in mineral poisonings, particularly by mercury and phosphorus. It usually begins at the margin of the gums of the lower jaw and extends to the cheeks and tongue. The gums become red and swollen and even hemorrhagic at the junction with the teeth, and change into a soft necrotic mass that bleeds easily. The epithelium is de-

stroyed and deep ulcers form; suppuration may ensue and the teeth become so loosened that they fall out, the jaw bone becomes exposed, infection occurs, and necrosis of the jaw follows. There is also an increased flow of saliva, accompanied by a bad odor. At the same time the general health is more or less affected, the patient becomes pale and loses weight. Mercury in too large doses or in small doses continued for too long a time may be the cause, and the condition is known as *salivation*.

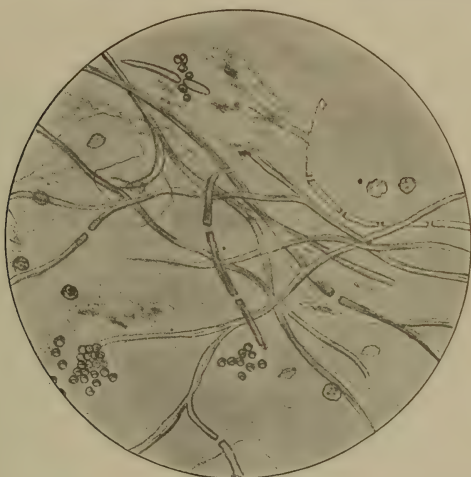


FIG. 74.—THRUSH FUNGUS, EPITHELIAL CELLS, AND LEUKOCYTES FROM A CHILD SUFFERING FROM ULCERATIVE STOMATITIS (Boston).

*Aphthous stomatitis* occurs usually in children who are in poor physical condition or who have not been taught how to take care of the mouth. It may occur in adults who are not well. On the mucous membranes of the mouth there appear small whitish spots surrounded by an inflammatory zone. These areas consist of degenerated epithelium and fibrin which may at times exfoliate, leaving small ulcers. This condition may last for some time, the exudate finally being absorbed and the epithelium regenerating.

*Thrush* is the form of micro-organismal stomatitis caused

by the *Oidium albicans* which involves those structures covered by squamous epithelium. This fungus does not seem to attack the normal mucous membranes, but becomes engrafted upon a mucosa that is the seat of some inflammatory disturbance. It usually occurs in marasmatic infants, but may be present in adults after or during acute fevers or chronic diseases with debility. The tongue is involved most frequently primarily,

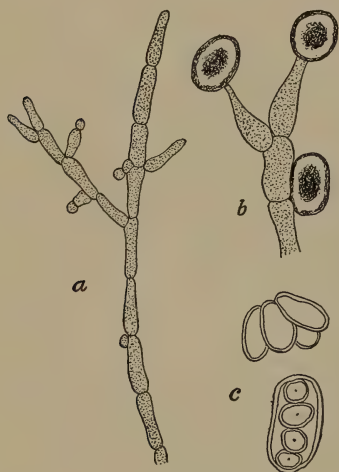


FIG. 75. — ENDOMYCES (OIDIUM) ALBICANS.

*a*, Filaments from a patch of thrush; *b*, terminal chlamydospores; *c*, asci and ascospores.

but secondary infections may develop through contact. There is at first a diffuse reddening of the mucous membrane, then the formation of patches of a shining, whitish false membrane that, although superficial, adheres at first rather tightly to the underlying tissue, but finally becomes looser. The membranous spots vary in size; at first the diameter rarely exceeds 4 to 5 mm. The patches may coalesce, forming large areas of a pseudomembrane that is composed of desquamated epithelium, extraneous organisms, and parasitic threads. If the membrane is removed, it soon reappears. The disease may spread from the tongue to

the pharynx and the esophagus, and it has been known to extend into the stomach and bronchi.

The *Oidium albicans* is a budding fungus resembling the yeast and forms long myceliæ. It can be cultivated upon acid media that contain sugar, but longer threads form when it is grown on alkaline media.

*Gangrenous stomatitis*, or *noma*, is a rapid necrotic process involving the mucous membrane of the cheek. It occurs in children between two and twelve years of age whose general

condition is extremely poor, either as the result of chronic or severe acute disease; it usually follows some of the acute infectious processes, particularly measles. It begins near the angle of the lip on the buccal surface as a livid area, at first hard and edematous, but rapidly becoming softer and gangrenous. Penetration through to the skin may occur or the process may remain localized in the mucous membrane and underlying tissues. By the time the skin is involved vesicles are formed and the tissue soon breaks down into a foul-smelling

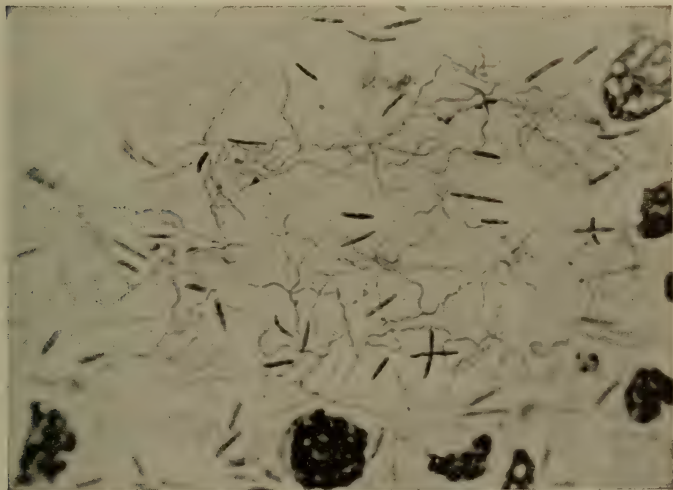


FIG. 76.—SPIROCHÆTA VINCENTI FROM CASE OF ULCERATIVE STOMATITIS ( $\times 1200$ ) (Todd).

mass. Hemorrhage is infrequent, probably the result of extensive thrombosis. Death from exhaustion and secondary infection usually follows. The slough may separate and the patient recover, with commonly marked deformity from the cicatrization. Although more common in female children, noma may occur in either sex at any age. No specific cause for this condition has been discovered. Many forms of bacteria have been found, but the more common type found is a spirillum or spirochete, possibly Vincent's fusiform organism.

*Syphilitic stomatitis* may occur either as the primary chancre or, what is more common, as the secondary mucous patch. The primary lesion may appear on the lip, tongue, or tonsil in either a soft or an indurated form, and is accompanied by enlargement of the lymph-nodes. Mucous patches may occur on any part of the mucous membrane, but are commonest on the lips and palate. They are irregular, superficial ulcers, frequently covered by a thin grayish pseudomembrane. They are painful, and the condition is usually associated with increased flow of saliva and a bad odor. Sometimes the local inflammatory condition gives rise to considerable thickening of the mucosa, this membrane becoming white or bluish-white in color. The area is usually small and is called *leukoplakia*; it may undergo eventually a malignant change, becoming cancerous. In the tertiary stage *gumma* may be found in the tongue or in the palate. They are generally small and are prone to undergo softening, with ulceration and subsequent cicatrization.

*Tuberculosis* may rarely be primary, but is usually secondary to infection from tuberculosis of the larynx or pharynx or by infected sputum. The posterior portion of the tongue is usually involved, small nodular tubercles of a yellowish-red color appearing. These soon degenerate, forming ulcers with thickened edges. The lesions may very closely resemble epithelioma.

*Actinomycosis* may result from the infection of an abraded surface by the fungus. It generally gains entrance to the alveolar portion of the jaw by way of carious teeth. The process is, as a rule, a slow one of swelling, with destruction of the adjoining tissues. There may accompany it a widespread involvement of the lymphatic nodes of the neck and jaw.

**Oral Sepsis.**—Under this term are included the various inflammatory conditions affecting the mouth and attended by manifest infection. According to Coplin, many believe that, in addition to the purely local influence exerted by septic processes involving the oral mucosa and gums (*gingivitis*), important secondary manifestations are not uncommon. Alveolar abscess, periostitis, suppurative inflammation of the antrum and nasal sinuses, tonsils, pharynx, and middle ear may be secondary to lesions primary in the buccal mucosa.

Local infection traveling by the lymphatics may implicate the submaxillary and anterior cervical lymph-nodes. Inflammation of the gastro-intestinal mucosa may be caused by pyogenic organisms which are primarily colonized in the mouth. Infection of the blood, manifested by pleurisy and other forms of serositis and even ulcerative endocarditis, may have a similar origin. Some contend that pernicious anemia is the result of oral sepsis. A form of alveolar inflammation, characterized by suppuration extending deeply into the sockets of the teeth, and called *pyorrhea*, or *pyorrhea alveolaris*, sometimes causes an acute suppurative inflammation, or occasionally necrosis, of the adjacent bone.

**Glossitis**, or inflammation of the tongue, occurs either in a superficial or a deep form and may be acute or chronic, diffuse or circumscribed. It may follow marked intestinal disorders or be the result of local irritations, such as the sharp edge of an ulcerated tooth or an ill-fitting dental plate. The surface of the tongue becomes white or brown, due to the degenerated epithelium, bacteria, and particles of food. It may become dry, hard, and fissured. If the superficial glossitis becomes chronic, local thickenings of the mucous membrane are formed. These are irregular, slightly elevated, whitish patches, which may spread and coalesce. This is known as *leukoplakia*, or *psoriasis linguæ*, and in the great majority of instances is probably syphilitic in origin. Occasionally the thickened epithelium may desquamate and leave an ulcer. Quite frequently secondary cancer (epithelioma) develops at the site of the lesion.

The deeper inflammations of the tongue usually result from injury and infection. The organ becomes swollen, painful, and infiltrated by leukocytes; small abscesses may form. This condition is usually accompanied by some degeneration and atrophy of the muscles.

One form of inflammation of the tongue is known as *melanoglossia*, black tongue. The epithelium upon the papillæ, particularly the filiform variety, becomes greatly increased and gives rise to a hairy appearance. The color may be due to an increase of pigment in the epithelium or to a fungus mixed with which are particles of food and bacteria.

**Tumors** of many kinds are found within the mouth. Of the connective-tissue forms, *lipoma*, *fibroma*, *myxoma*, and *sarcoma* occur; also *lymphangioma* and *hemangioma*. *Adenoma* and *carcinoma* of the squamous type are found. *Sarcoma* generally appears upon the gums near the roots of the teeth and is known as an *epulis*; is usually composed chiefly of spindle cells with giant cells more or less numerous. The term "epulis" may be applied to pure fibroma. *Carcinoma* is, as a rule, present in the form of the squamous epithelioma. It is found most commonly on the tongue, near the tip, but to one side. It frequently occurs at the site of a long-continued ulceration from a carious tooth. There appears a circumscribed, hard swelling which soon breaks down and ulcerates rapidly. The neighboring cheek and larynx may soon be involved and metastases occur in the cervical and submaxillary lymph-nodes. The growth is usually rapid and, if excised, quickly returns. This lesion frequently resembles syphilitic conditions and occasions difficulty in making a diagnosis.

*Cysts* may result from obstruction to the ducts of the mucous or salivary glands. A *ranula* is a cystic dilatation of Nuhn's glands situated under the tip of the tongue, which may be displaced backward and upward. A thick viscid fluid fills the cavity. *Dermoid* cysts and cysts of the embryonal branchial clefts may involve the mouth.

*Macroglossia*, thickening of the tongue, and *macrocheilia*, thickening of the lips, result from a lymphangioma. The lymphatic spaces are much distended and contain liquid and lymphoid cells. This condition is generally congenital, being due to a deficiency in the amount of thyroid secretion. It occurs chiefly in cretins.

## THE TONSILS

Anemia and hyperemia occur here just as elsewhere. Active hyperemia as a beginning of inflammation; passive, in chronic heart and lung disease, in which cases the veins may be distinctly varicose. Edema is found in connection with inflammation and ulceration, and may be quite marked. Hemorrhage may occur in purpura and in severe infectious fevers,

as well as being the result of direct injury. At times the blood may form quite a tumor between the layers of the soft tonsil.

**Tonsillitis**, or inflammation of the tonsil, may be either acute or chronic. *Acute tonsillitis* may be symptomatic either of various diseases or it may be a true local primary condition as a consequence of direct infection. According to the degree of inflammation, this condition may be *catarrhal*, *lacunar* or *follicular*, and *phlegmonous*. In the *catarrhal* type the tonsils are somewhat swollen and reddened and the condition is usually an accompaniment of a catarrhal pharyngitis. The *lacunar* or *follicular* form is characterized by the presence of many small yellowish-white spots over the surface of the tonsil. Each spot represents a follicle that has become filled with an exudate made up of degenerated epithelium and bacteria, as staphylococci, streptococci, pneumococci, or tubercle bacilli. The exudate from the lacunæ may extend over the surface of the tonsil, forming a covering that resembles the diphtheric pseudomembrane. The exudate within the lacunæ may become dry and lime salts be deposited. If the infection passes through the crypts to the deeper tissues, *phlegmonous* tonsillitis may result. In this there is abscess formation as well as round-cell infiltration. These collections of pus may discharge into the mouth, open into the larynx or even involve the large vessels of the neck, perforation of the carotid having occurred.

Recent investigations into the bacteriology of tonsillitis indicate that many of the general infections of the body are secondary to the entrance of the organisms through the tonsils. The acute inflammatory rheumatic conditions, accompanied by severe involvement of the joints and of the heart, are evidently the result of tonsillar invasion. These structures are also suspected of being the portals by means of which the tubercle bacilli gain entrance into the cervical lymph-nodes.

In *chronic tonsillitis* there is an increase in the size of the tonsils, due not only to a hyperplasia of the connective-tissue septa and reticulum, but also to an increase in the lymphoid follicles themselves. The tonsils may become so hypertrophic

as to almost meet in the middle line, and by so doing causé obstruction to breathing and swallowing.

This form is frequently accompanied by marked disturbances of the general health and development. It is often present in children, and as a result they breathe with their mouths open; their digestion is often impaired and their mentality may be distinctly below normal. Another common result of this condition is an interference with the proper development of the upper jaw and nasal cavities. The upper jaw may be distinctly narrowed, thus causing more or less deformity with displacement and irregularities of the teeth. The enlarged tonsils should be removed at an early age before the bony tissues have become so hardened as to prevent corrective measures.

Instead of the above hypertrophic form, the involvement may be confined to the lacunæ, which are wider and deeper than normal. They become filled with an exudate that through decomposition can give rise to inflammatory processes in adjacent tissues.

*Tonsillitis leptothricia* is caused by infection of the tonsils by the *Leptothrix buccalis*. It usually occurs in those in poor condition, but may be found in strong, well-nourished individuals. Over the surface of the tonsil are numerous spots covered by a thick, dense, dry, whitish exudate that is composed of masses of threads of the leptothrix. This is firmly adherent to the crypts and is removed with difficulty. It usually involves other portions of the pharynx, but does not occasion much inflammation in the surrounding tissues. It tends to run a chronic course, not yielding readily to treatment.

*Tuberculosis* of the tonsils is not uncommon. It is generally due to primary infection, and then involves the cervical lymph-nodes secondarily. From there it may by extension gain access to the lungs and occasion tuberculosis within them. Secondary involvement of the intestines may also occur.

*Syphilis* of the tonsils may occur as a primary, secondary, or tertiary lesion.

## PHARYNX

*Circulatory disturbances* are usually a part of similar troubles of neighboring tissues.

**Inflammation.**—The *acute catarrhal pharyngitis*, or *angina*, may result from exposure to cold, to the irritating action of various substances, as tobacco smoke, dust, chemicals, or may occur as part of some intestinal derangement. The mucous membranes become red and swollen, with, at first, decreased secretion. As the process goes on there is frequently an abundance of a thick tenacious secretion composed of mucus and desquamated columnar epithelial cells. In severe cases true ulcers may form along the posterior wall.

In *chronic pharyngitis*, such as occurs in excessive smokers and in those who use their voice a great deal, the posterior wall and the faucial pillars are involved particularly. There is a chronic congestion and the lymphoid collections become hyperplastic, causing slight granular elevations. The secretions become less, as a rule, but they may be increased in amount and mucopurulent in character. The pharyngeal tonsils are usually hyperplastic.

*Phlegmonous pharyngitis* and *retropharyngeal abscess* follow the entrance of bacteria, usually pyogenic, into the deeper tissues, or may result from caries of the spinal column. If the abscess formation is rapid, there is bulging into the pharynx and rupture may take place. If the process has been slower, the pus may extend along the deep fascia until perforation into the posterior mediastinum, bronchi, or esophagus occurs. General septicemia not infrequently occurs.

*Syphilitic pharyngitis* is common as a secondary symptom, but it has no characteristic appearance that renders it easily recognizable.

*Tuberculous pharyngitis* is unusual, but when present is generally secondary to tuberculosis of the lungs.

*Pseudomembranous pharyngitis* may be diphtheritic or non-diphtheritic.

The *non-diphtheritic* pharyngitis is generally caused by the *Streptococcus pyogenes*, or may result from the action of very

irritating substances, such as steam or ammonia. The appearance of the pseudomembrane in such cases is, to the naked eye, similar to that of the diphtheric variety. It, however, is not accompanied by the same constitutional depression, is not followed by paralyses, nor is the characteristic bacillus found.

*Diphtheritic pharyngitis* is caused by the Klebs-Löffler bacillus and is characterized by a pseudomembrane that is yellowish or dirty gray in color. The involvement may be limited to a small portion of the pharynx, being most common on the arches of the fauces, but the tonsils and nares as well may be affected. It may extend even into the esophagus and stomach.

This pseudomembrane is laminated, being composed of fibrin in the meshes of which are desquamated epithelial cells, leukocytes and erythrocytes, and the diphtheria bacilli in great numbers. It is formed by the coagulation of the exudate and by coagulation necrosis of the superficial tissues. This membrane can be peeled off, exposing a raw ulcerated surface upon which a new membrane quickly forms. The lymph-nodes near by may enlarge and undergo suppuration, probably due mainly to the presence of pyogenic cocci.

The extent of the pseudomembrane does not necessarily denote the gravity of the infection. The severity depends upon the ability of that particular strain of diphtheria bacilli to form toxin. The clinical symptoms are the manifestations of the intensity of the toxin present. In severe forms the membrane may spread rapidly, and if there is a mixed infection with streptococci, hemorrhage and even local gangrene may result, as well as secondary abscess formation elsewhere in the body. Besides the local manifestations there are marked general symptoms due to the presence of a dangerous toxin. The action of this substance is seen in the form of small foci of necrosis in various tissues of the body. Death may result from cardiac paralysis due to the action of the toxin.

Of the internal organs, the liver especially shows focal necrosis in which the cells are degenerated, the nuclei showing hyperchromatosis. There is also hyperemia of the kidney, with cloudy swelling of the epithelium, edema, and even hemorrhage. Inflammation of the heart muscle (myocarditis) and degenera-

tion of the cardiac muscle also occur. The spleen is commonly hyperemic.

During convalescence, paralysis, particularly of the throat, may occur, also of the muscles of the eyes, the larynx, and the diaphragm. The muscles will show a round-cell infiltration between the fibers, and a granular and fatty change of the cells.

There may be degeneration of the ganglion cells of the cord.

**Vincent's angina** is an infection of the pharyngeal mucous membrane due to the presence of fusiform bacilli and spirochetes. The disease differs from an ordinary acute pharyngitis due to streptococci or staphylococci in that the constitutional symptoms are less severe and that there is a great tendency to ulcerations. The submaxillary glands may be swollen.

**Tumors** of the pharynx are rare. Squamous epithelioma as a result of extension is the most common, but fibroma and sarcoma have been observed.

### SALIVARY GLANDS

**Inflammation** of the parotid gland, *parotitis* or *mumps*, occurs as a primary disease, evidently due to some bacterium. The infection probably occurs by way of the parotid duct. The gland becomes much swollen and tense on account of a marked serous exudation. Although abscess formation may seem imminent, it is very unusual for suppuration to occur. The exudate may be absorbed and the gland very quickly return to its normal condition. Sometimes a chronic induration may remain or, if abscess formation with rupture has occurred, a fistula may result. Secondary involvement of the testicles or ovaries may occur either during the attack or shortly after the primary inflammation has subsided. The infecting agent is evidently in the sputum.

*Suppurative parotitis* is not uncommon in the inflammation of the parotid gland secondary to infectious diseases, as typhoid, scarlet fever, and diphtheria. Small abscesses may form and become confluent. The interstitial tissue of the gland is more or less infiltrated with pus-cells, and the parenchyma cells may undergo fatty degeneration. The inflammation may be con-

fined to the gland or it may spread to adjacent parts, sometimes causing much destruction of tissues. It may give rise to inflammation of the brain or of the inner ear, or even to metastatic pyemic abscesses in different parts of the body. The condition may become chronic, with hyperplasia of the fibrous connective tissue, or it may subside and leave no traces.

**Ludwig's angina** is a very severe form of inflammation of the submaxillary gland. The infection extends into the surrounding tissues with suppuration that may extend beneath the tongue and jaw, and to the structures around the larynx and pharynx. Sometimes the cellular tissue of the neck may be involved. Abscesses may form and discharge either externally or into the mouth. Necrosis and gangrene are commonly present and death frequently occurs. This condition may follow infection by means of carious teeth or involvement of the gland itself during the course of an infectious disease, particularly scarlet fever.

**Fistulæ** of the salivary ducts may follow traumatism or the perforation of an abscess. The parotid duct is the one generally involved.

**Concretions**, or calculi, are sometimes found and are called *sialoliths*. They are composed of phosphate and carbonate of calcium, and occur in the smaller as well as in the main ducts. They frequently give rise to retention cysts, the most common variety being that known as *ranula*, a term applied not only to a cystic condition of Nuhn's glands, but of the sublingual as well.

**Tumors** of the salivary gland are not uncommon, the parotid being the one most frequently involved; the connective-tissue tumors, as fibroma, lipoma, chondroma, and sarcoma, being the most usual. Adenoma and primary carcinoma are infrequent. The most common neoplasm is the *mixed tumor* of the parotid. This is composed mainly of undeveloped connective tissue, but includes cartilage and mucous and fibrous tissues. It grows slowly, seldom gives rise to metastasis, and, when excised, rarely returns. It is probably the result of inclusions taking place in fetal life during the closure of the first branchial cleft. Typical *endotheliomata*, usually of the lymph-vessel type, are also encountered.

## CHAPTER XI

### BACTERIA

THESE organisms are of interest in that they may be parasitic upon and within the body of man, of the lower animals, and other plants. The less important ones will be presented first, the bacteria being discussed more fully later; these latter being especially important on account of their relation to disease and their bearing upon general hygiene and preventive medicine.

### THE YEASTS

The yeasts, *blastomycetes* or *saccharomycetes*, are unicellular fungi which multiply by budding, in which naked asci (spore cases) are formed freely on the mycelium. The yeast cell is, as a rule, oval, but among the wild yeasts, or *torulæ*, spheric forms are common. Great variations occur in size, yeasts measuring usually from 10 to 20  $\mu$  in length, with a width of about one-half or two-thirds of the long diameter. They possess a well-defined, doubly contoured cell-membrane, composed chiefly of cellulose, and the cytoplasm, unlike that of the bacteria, shows definite structure. These organisms multiply by *budding*, at which time the mother-cell sends out a small globular projection of the cell membrane into which maternal cytoplasm flows. This bud gradually enlarges until it becomes about the same size as that of the original cell. Finally, by the gradual narrowing of the isthmus connecting the two, the daughter-cell becomes complete and free. When the surrounding conditions are unfavorable most yeasts are able to form spores. These, called "ascospores," are formed within the yeast cell itself, each spore forming a separate membrane of its own, but all of them lying well protected within the original cell-membrane.

In this family Besson includes the following parasitic yeasts: the *Endomyces albicans* (*Oidium albicans*), the parasite of

*thrush*; the *Cryptococcus dermatitis* (*Blastomyces dermatitis*), the cause of a form of chronic dermatitis; and the *Saccharomyces tumefaciens*.

### THE MOLDS

In this group, the *hyphomycetes*, may be included many organisms having in common the formation of a well-marked mycelium, but differing so greatly in other respects as to be placed in widely separated groups in the systematic arrangement of the fungi. The characteristic feature of this class is the formation of long, interlacing filaments or threads, known as mycelia. From these there extend branches called hyphæ. In this class may be placed the *Achorion schönleini* (the parasite causing *favus*), the *Trichophyton* and *Microsporon*, the *Mucor*, the *Aspergillus*, and *Eurotium*. These parasitic organisms are described in detail under the headings of the diseases caused by them.

### THE HIGHER BACTERIA

This group occupies an intermediate position between the true bacteria and the molds. These organisms are characterized by filamentous forms with real or apparent branchings. The filaments are usually divided transversely, appearing as if composed of bacilli. The free ends only seem to be endowed with the ability to reproduce, and they develop peculiar elements that differentiate the higher from the other bacteria, whose cells are all equally free and independent.

*Leptothrix*.—These comprise long threads which do not branch, and are at times separated with difficulty from chains of bacilli. They rarely cause trouble, but have been observed in connection with inflammations of the mouth and pharynx, particularly along the edges of the tonsillar crypts, where they grow with the formation of persistent white patches. Cultivation of the *leptothrix* is difficult.

*Cladothrix* is a thread-like form in which false branching may be recognized, an appearance resulting from the fragmentation of the threads. The terminal cell breaks away from the main stem, is set at an angle by the elongation of the thread itself, and, as both continue to divide, the simulation of true

branching is produced. This type is probably not pathogenic; most of the cases ascribed to this class were likely due to streptothrix infection.

*Streptothrix* denotes forms with numerous true branches and spores which usually appear in chains. Numerous cases of disease have been reported as being caused by these organisms.

*Actinomyces* is characterized by the formation of club-shaped ends and the radiating arrangement of the threads. This organism causes a specific disease of the lower animals, sometimes transmitted to the human being.

## BACTERIA

Bacteria are minute unicellular organisms, probably belonging to the vegetable kingdom, the *schizomycetes*. It is difficult to classify them, but probably the best arrangement is a modification of Migula's method as follows:

### CLASSIFICATION OF THE BACTERIA

#### I. ORDER: EUBACTERIA (True Bacteria)

##### A. SUB-ORDER: Haplobacteria (Lower Bacteria)

- I. Family COCCACEÆ. Cells globular, becoming slightly elongate before division. Division in one, two, or three directions of space. Formation of endospores very rare.

##### (A) Without flagella.

1. *Streptococcus*. Division in one direction of space, producing chains like strings of beads.
2. *Micrococcus*. Division in two directions of space, so that tetrads are often formed.
3. *Sarcina*. Division in three directions of space, leading to the formation of bale-like packages.

##### (B) With flagella.

1. *Planococcus*. Division in two directions of space, like micrococcus.
2. *Planosarcina*. Division in three directions, like sarcina.

- II. Family BACTERIACEÆ. Cells more or less elongate, cylindric, and straight. They never form spiral windings. Division in one direction of space only, transverse to the long axis of the cell.

##### (A) Without flagella.

1. *Bacterium*. Occasional endospores.

##### (B) With flagella.

2. *Bacillus*. Flagella arising from any part of the surface. Endospore formation common.
3. *Pseudomonas*. Flagella attached only at the ends of the cell. Endospores very rare.

III. Family SPIRILLACEÆ. Cells twisted spirally like a corkscrew, or representing sections of the spiral. Division only transverse to the long diameter.

1. *Spirosoma*. Rigid; without flagella.
2. *Microspira*. Rigid; having one, two, or three undulating flagella at the ends.
3. *Spirillum*. Rigid; having from five to twenty curved or undulating flagella at the ends.
4. *Spirochæta*.<sup>1</sup> Serpentine and flexible. Flagella not observed; probably swim by means of an undulating membrane.

#### B. SUB-ORDER: Trichobacteria (Higher Bacteria)

IV. Family MYCOBACTERIACEÆ. Cells forming long or short cylindric filaments, often clavate-cuneate or irregular in form, and at times showing true or false branchings. No endospores, but formation of gonidia-like bodies due to segmentation of the cells. No flagella. Division at right angles to the axis of rod in filament. Filaments not surrounded by a sheath as in Chlamydo-bacteriaceæ.

1. *Mycobacterium*. Cells in their ordinary form, short cylindric rods often bent and irregularly cuneate. At times Y-shaped forms or longer filaments with true branchings may produce short coccoid elements, perhaps gonidia. (This genus includes the *Corynebacterium* of Lehmann-Neumann.) No flagella.
2. *Actinomyces*. Cells in their ordinary form as long branched filaments; growth coherent, dry, or crumpled. Produce gonidia-like bodies. Cultures generally have a moldy appearance, due to the development of aerial hyphæ. No flagella.

V. Family CHLAMYDOBACTERIACEÆ. Forms that vary in different stages of their development, but all characterized by a surrounding sheath about both branched and unbranched threads. Division transverse to the length of the filaments.

1. *Cladothrix*. Characterized by pseudodichotomous branchings. Division only transverse. Multiplication by the separation of whole branches. Transplantation by means of polar flagellated swarm-spores.
2. *Crenothrix*. Cells united to form unbranched threads which in the beginning divide transversely. Later the cells divide in all three directions of space. The products of final division become spheric, and serve as reproductive elements.
3. *Phragmidiothrix*. Cells at first united into unbranched threads. Divide in three directions of space. Late in the development, by the growth of certain of the cells through the delicate, closely approximated sheath, branched forms are produced.
4. *Thiothrix*. Unbranched cells inclosed in a delicate sheath. Non-motile. Division in one direction of space. Cells contain sulphur grains.

<sup>1</sup> The spirochæta and some closely related forms are now thought to be more properly classified among the protozoa than among the bacteria.

## II. ORDER: THIOBACTERIA (Sulphur Bacteria)

I. Family BEGGIATOACEÆ. Cells united to form threads which are not surrounded by an inclosing sheath. The septa are scarcely visible. Divide in one direction of space only. Motility accomplished through the presence of an undulating membrane. Cells contain sulphur grains.

There are two families, numerous subfamilies, and thirteen genera in this order. They are all micro-organisms of the water and soil, and have no interest for the medical student.

A more common but less accurate method of classification divides bacteria into:

1. *Bacillus*.—A rod-shaped organism that is not curved or twisted upon itself, one diameter being distinctly greater than the other.

2. *Micrococcus* or *Coccus*.—A minute spheric organism.

(a) *Diplococcus*, when occurring in twos.

(b) *Streptococcus*, when occurring in chains.

(c) *Staphylococcus*, when in bunches like grapes.

(d) *Tetracocci*, when division takes place in two directions, and the individuals remain attached in groups of four.

(e) *Sarcina*, when dividing in three directions, giving rise to bale-like packages.

(f) *Zoöglea*, when grouped in irregular masses.

3. (a) *Spirillum*.—An organism twisted like a corkscrew and rigid; usually has polar flagellæ.

(b) *Spirochæta*, when the organism is long, slender, flexible, and without flagella.

(c) *Vibrio*.—A short organism, bent like a comma, usually with a single end-flagellum.

**Structure.**—Bacteria are composed of a small amount of cytoplasm surrounding a large but indistinctly defined nucleus. In this cytoplasm may be found granules of fat, pigment, sulphur, etc. Each cell is surrounded by a distinct cell-wall, and sometimes there is present a peculiar gelatinous material forming a capsule.

**Motility.**—The greater number of bacteria are non-motile, but many possess the power of motility as a result of the presence of flagella. Most of the cocci are non-motile. According to

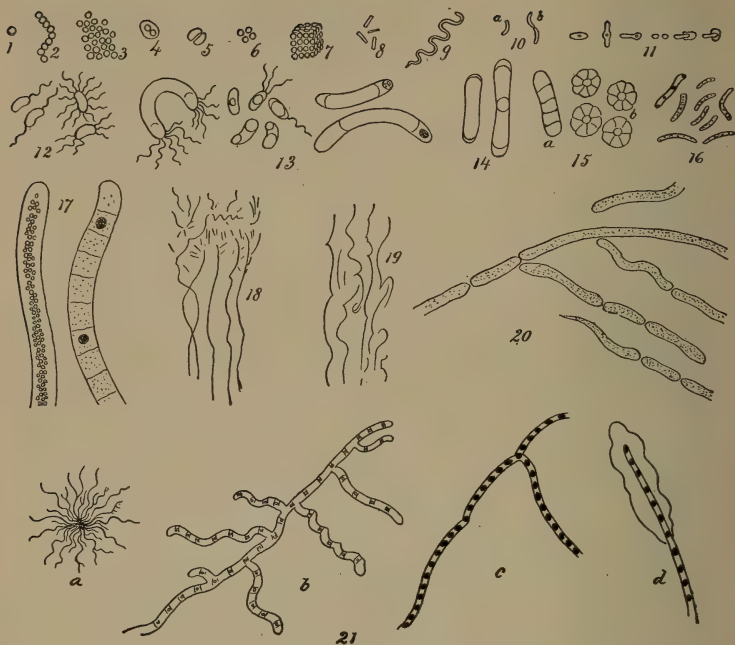


FIG. 77.—TYPES OF MICRO-ORGANISMS.

1, Coccus; 2, streptococcus; 3, staphylococcus; 4, capsulated diplococcus; 5, biscuit-shaped coccus; 6, tetrads; 7, sarcina form; 8, types of bacilli (1 to 8 are diagrammatic); 9, non-septate spirillum ( $\times 1000$ ); 10, ordinary spirillum: (a) comma-shaped element; (b) formation of spiral by comma-shaped elements ( $\times 1000$ ); 11, types of spore formation; 12, flagellated bacteria; 13, changes in bacteria produced by plasmolysis (after Fischer); 14, bacilli with terminal protoplasm (Bütschli); 15, (a) *Bacillus* composed of five protoplasmic meshes; (b) protoplasmic network in micrococcus (Bütschli); 16, bacteria containing metachromatic granules (Ernst Neisser); 17, *Beggiatoa alba*—both filaments contain sulphur granules—one is septate; 18, *Thiothrix tenuis* (Winogradski); 19, *Leptothrix innominata* (Miller); 20, *Cladothrix dichotoma* (Zopf); 21, *Streptothrix actinomyces* (Boström): (a) colony under low power; (b) filament showing true branching; (c) filament containing coccus-like bodies; (d) filament with club at end.

the presence or absence of flagella, the following classification of bacteria has been made:

1. *Gymnobacteria*, forms without flagella.

2. *Trichobacteria*, forms with flagella.

(a) *Monotricha*, a single flagellum at one end.

(b) *Leptotricha*, a bundle of flagella at one end.

(c) *Amphitricha*, a flagellum at each end.

(d) *Peritricha*, flagella arising from all parts of the surface of the organism.

**Size.**—Bacteria are so minute that a special unit has been adopted for their measurement. This is the micromillimeter ( $\mu$ ), or one-thousandth part of a millimeter, known as the *micron*. It is equivalent to the one-twenty-five-thousandth part of an inch. The size of bacteria vary from a fraction of a micromillimeter to 20 or even 40 micromillimeters.

**Reproduction.**—*Fission.*—The most common method in which the organisms divide into two. This occurs very rapidly if there is enough nutritive material present and the surrounding conditions are favorable, the length of a generation varying from fifteen to forty minutes.

*Sporulation* occurs when the conditions do not favor multiplication. There are then formed small, round or oval, highly refracting bodies called *spores*, which are capable of resisting very unfavorable surroundings. They differ from bacteria in being able to withstand evaporation and exposure to quite high degrees of heat. Few adult bacteria can resist temperatures above  $70^{\circ}$  C., but spores are uninjured by such heat and may even resist the temperature of boiling water ( $100^{\circ}$  C.) for a short time. If the spore develops within the bacterium in the middle, or at one or other of the ends, it is called an *endospore*. If the spore is so large as to cause a bulging of the organism it is called a *clostridium*. These forms occur in the bacilli. Among the micrococci there are times when the entire organism is transformed into a spore, an *arthrospore*.

*Germination of Spores.*—When conditions become favorable the spore may develop into an adult organism. Its contents, which have been clear and transparent, become granular, the body increases slightly in size, the capsule becomes less distinct, and in the course of time splits open to allow the escape of the young organism. This begins to increase in size, develops

its characteristic capsule, and presently begins to multiply by fission.

**Growth of Bacteria.**—In the cultivation of bacteria there are many conditions that can influence the growth favorably or unfavorably. There are, however, certain factors that are really essential.

**Food.**—Bacteria grow best when diffusible albumins are present, but carbohydrates will do. It has been found that the food requirements differ very greatly with the different kinds of organisms. Some will live in water to which an extremely small amount of organic matter has been added. Others require a concentrated medium such as blood-serum. Then, too, the addition of certain substances, such as glucose or glycerin, may exert a very favorable influence.

**Oxygen.**—All micro-organisms must have oxygen in order to continue to live, but it may be present either in the free or in a combined condition. Those organisms which grow in the presence of free (uncombined) oxygen are known as *aërobes*. Those which will not grow in the presence of free oxygen are the *anaërobes*. There are, however, some of the aërobic type which will grow about as well without free oxygen as with it; these are the *optional* (facultative) *anaërobes*.

**Moisture** to some degree is an absolute necessity, but it may be present in very slight amount. Unless some is present nearly all organisms will dry up and cease to multiply, but spores may be formed first and persist more or less indefinitely. In making up artificial culture-media there should be present at least 80 per cent. of water.

**Temperature** of a proper degree is of the greatest importance. Every micro-organism grows best at some definite degree of heat, and shows variations in its activity as the temperature changes. The organisms, however, may be able to endure extreme degrees of cold without being destroyed—some can be placed in liquid air and yet undergo multiplication when the temperature is raised. They cannot, as a rule, stand the higher temperatures as well, although a few varieties of organisms may thrive at high degrees ( $65^{\circ}$ – $70^{\circ}$  C.). They are called *thermophilic*, and are found in manure piles and hot springs.

The temperature at which micro-organisms grow best is known as the *optimum*; the lowest temperature at which they continue to multiply, as the *minimum*; the highest at which they remain active, the *maximum*. With pathogenic or disease-producing organisms the optimum temperature is that normal to the body ( $37^{\circ}$  C.).

A temperature of from  $50^{\circ}$  to  $60^{\circ}$  C. will weaken and finally destroy nearly all forms. If they are exposed to steam or boiling water at the temperature of  $100^{\circ}$  C. all fully developed bacteria will be killed in a few minutes, but their spores may be able to resist this heat for a longer time. When dry heat is used a higher temperature is required. The spores may withstand  $150^{\circ}$  C. for an hour or  $175^{\circ}$  C. for five to ten minutes.

*Reaction*.—Most true bacteria grow best in neutral or feebly alkaline media, although some grow well in strong acids and others in marked alkalinity.

Many chemical bodies will restrain the growth or destroy the bacteria. These substances may be produced by the bacteria in their growth or they may be artificially introduced. Those which will restrain the growth but not kill are called *antiseptics*; those that kill, *germicides*.

*Light*, particularly the direct rays of the sun, will retard bacterial growth and in many cases kill the organisms. Certain colors distinctly retard growth, blue being the most effective. A weak, diffused light seems most favorable, but various organisms react differently, certain bacteria producing color only when exposed to the ordinary light of a room, while others will produce color only in the dark.

*Motion*.—Bacteria apparently grow best when there is an absence of motion.

*Electricity* and *x-rays* do not seem to have any constant effect upon bacteria.

*Symbiosis*, or the association of one organism with another, may cause an increase in its activity, as the growth of the tetanus bacillus in the presence of other bacteria that use up the supply of oxygen. *Antibiosis* is the condition in which the association may be detrimental to one of the organisms.

**Products of Bacterial Growth.**—According to the substances formed as a result of their growth bacteria may be divided into:

*Zymogens*, bacteria of fermentation.

*Saprogens*, bacteria of putrefaction.

*Chromogens*, bacteria which produce colors.

*Photogens*, phosphorescent bacteria.

*Aërogens*, gas producers.

*Pathogens*, bacteria which produce disease.

Bacteria through their activity split up complex organic substances into simple compounds.

*Fermentation* is the splitting up of carbohydrates by the activity of the micro-organisms. This is the process that takes place in the formation of alcohol as a result of the action of yeast. Other forms of fermentation are those in which acetic, lactic, or butyric acids result.

*Putrefaction* is the breaking up of nitrogenous compounds by micro-organisms that can live only in dead organic substances. The albumins are first transformed into peptones, which split up into gases, acids, bases, and salts.

The albumins may become changed to toxalbumins or into alkaloidal substances called *ptomains*, which are “chemical compounds, basic in character, formed by the action of bacteria upon organic matter.” Ptomains are generally formed outside of the living body and cause harm only when introduced within it.

*Toxins* and *toxalbumins* are poisonous substances elaborated by bacteria during growth, and it is upon them that the disease-producing power of the organism rests.

The *bacterioproteins* also belong to this same group. These bacterial products are destroyed by sunlight, by heating to 60° to 80° C., by long keeping, and by the gastric juices. Tuberculin is an exception, in that it remains unaltered at a temperature of 100° C. The poisonous bodies may be either soluble or insoluble, and are generally peculiar to the variety of organism by which they are formed. Certain ones select definite cells upon which they act, and are called *specific*. Others, having no special selective powers, are *non-specific*.

*Chromogenesis*.—Bacteria that produce colored colonies or give a color to the medium in which they grow are called *chromogenic*; those producing white or no color, *non-chromogenic*. Most chromogenic organisms are saprophytic and non-pathogenic; but some of the pathogenic forms may produce color. Almost all known colors may be formed by different bacteria, and sometimes one organism will form two or more colors. The formation of the pigment probably depends upon the presence of oxygen.

*Aërogenesis*.—During fermentation and decomposition various gases are given off, such as carbon dioxid, sulphureted hydrogen, ammonia, etc.

Other enzymes formed by bacteria may cause the coagulation of milk and the liquefaction of gelatin. Some bacteria liquefy the gelatin in such a peculiar and characteristic manner as to make the appearance a valuable guide for the differentiation of species.

*Pathogenesis*.—Those micro-organisms which cause disease are called *pathogenic*; those that do not, *non-pathogenic*. There is, however, no sharp line between the two, as under adverse cultural conditions the pathogens may lose their ability to produce disease. On the other hand, those that are usually harmless may be made virulent.

## CHAPTER XII

### STERILIZATION AND DISINFECTION

IN all bacteriologic work the underlying factor of success is that no organisms, other than those with which we are working, should gain entrance into the utensils or materials used, or that they should be destroyed if present. Inasmuch as bacteria are always present in the dust, we must be constantly on guard. If no living matter is present in any of the articles used, they are said to be *sterile*.

By *sterilization* is meant the destruction or removal of all forms of micro-organisms. *Disinfection* refers to the destruction of the infectious organisms alone. A *germicide* is any substance that will kill germs. An *antiseptic* is a substance that will prevent the growth of micro-organisms, but will not necessarily kill them.

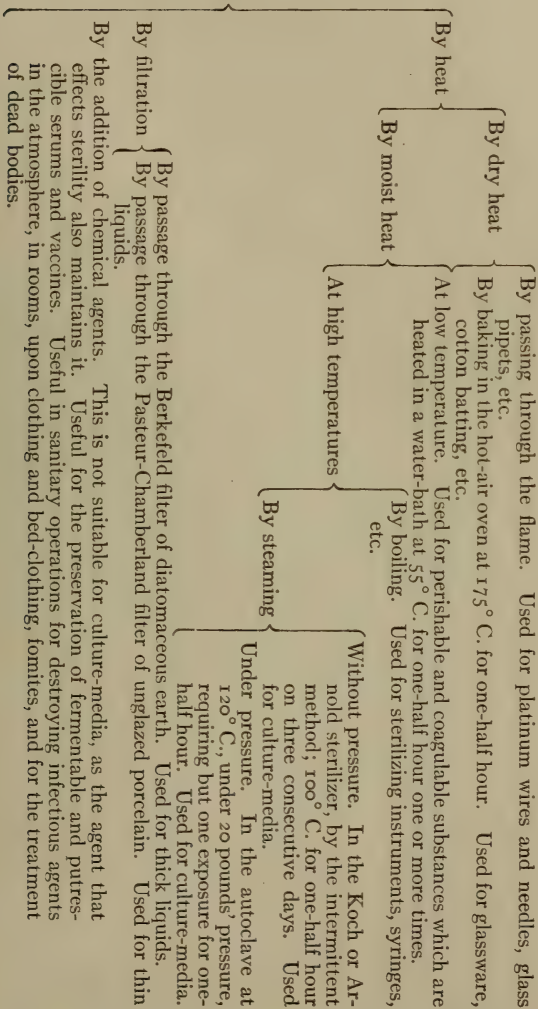
The table on page 193, from McFarland, gives in brief the various ways by which different materials may be sterilized.

It should be remembered that a higher temperature is required when dry heat is used than when there is moisture present. Although most adult bacteria are killed by a temperature of 60° C., the spores may resist 100° C. as long as an hour. Consequently, a much higher temperature must be employed in order that all forms may be destroyed. The platinum wires used for the inoculation of culture-tubes are sterilized by being held in the direct flame until incandescent. Care should be taken to sterilize the handle, lest micro-organisms from it might contaminate the cultures.

After the culture-tubes have been cleaned and dried, they are stoppered with plugs of *non-absorbent* cotton and then placed in the hot-air sterilizer. Although the tubes are sterilized the real purpose is to so mold the plugs that when removed from the tubes they will retain their shape.

## STERILIZATION

## Sterilization



**Sterilization of Culture-media.**—For this purpose dry heat cannot be used, as it would cause the water, some 80 per cent., to evaporate and the media would be dry and useless. Consequently, steam must be employed, but as the temperature of  $100^{\circ}$  C. does not kill the spores, it is necessary that the media be exposed more than once. The method employed is known as *intermittent sterilization*; the apparatus used is the Arnold sterilizer. In this method the materials to be sterilized are

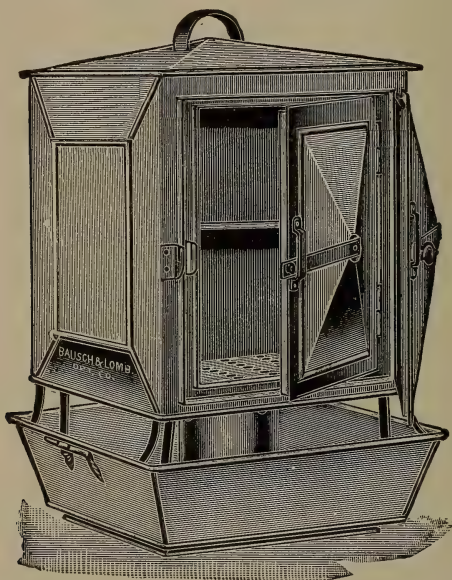


FIG. 78.—ARNOLD'S STEAM STERILIZER (Boston Board of Health form).

exposed to steam for fifteen to thirty minutes; they are then allowed to cool and stand for twenty-four hours. At the end of this time the heating is repeated, and after another interval of twenty-four hours they are exposed once more to the steam. Those spores that may have survived the first heating will have had time to develop into adult organisms and will be destroyed the second time. The third heating is largely a matter of precaution.

Another method of sterilization is that known as *pasteurization*. In this the substances to be sterilized are exposed to a temperature of from  $60^{\circ}$  to  $70^{\circ}$  C. for about one hour. This form, however, is not suitable if the organisms are spore formers. It is commonly employed in the commercial handling of milk.

When time is an important element, and the media used can resist high temperature, sterilization by means of the *autoclave* is most satisfactory. This instrument is a metal cylinder with a top that can be screwed down tight. Into this is placed about 1 liter of water, the culture-media is placed on shelves, the lid closed, and a Bunsen burner placed beneath. In this way, as the steam is under pressure, a temperature of  $110^{\circ}$  C. is soon obtained. Exposure to this for about one-half hour will destroy all spores as well as adult bacteria.

When the sterilization is completed, if "slant" cultures are to be made, the test-tubes are so placed that the medium will come about half-way up the side of the tube. When the media have solidified, the tubes can be kept in a moist condition for a longer period if the excess of the cotton plugs is trimmed off and rubber caps be put over the ends.

Some liquids may be sterilized by being passed through special *filters*, those having openings so minute that the fluid can pass through, but not the micro-organisms.

**Disinfection in General.**—There are many solutions of various substances that are used for disinfecting, but it is necessary to understand the limitations of many of these substances

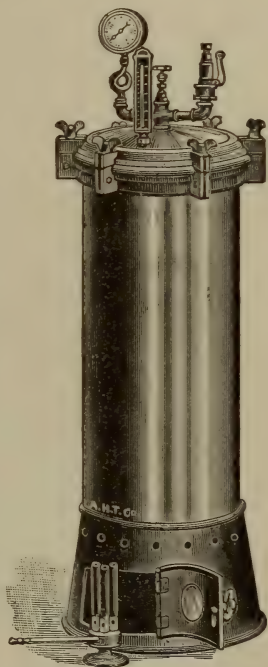


FIG. 79.—MODERN AUTOCLAVE.

in order to obtain proper results. *Bichlorid of mercury* (mercuric chlorid) is the most popular of the germicides for general use, as it is active, soluble, and cheap. It has, however, certain very marked disadvantages, it is very poisonous, is destructive to metal instruments, and is readily converted into a harmless compound if it comes in contact with albuminous matters. This latter fault may be corrected by adding to the mercuric solution a weak acid—as tartaric. Most of the mercuric tablets as purchased are combined with some acid. For application to the skin solutions of from 1:1000 to 1:2000 should be used; for large wounds and cavities, 1:10,000 to 1:5000; for small wounds, 1:2000.

*Carbolic acid* is not as reliable as mercuric chlorid, but it quickly destroys pus-organisms. It is readily soluble, is not affected by albuminous compounds, and does not injure metal instruments. It is quite poisonous and causes a local numbing of the tissues with which it comes in contact. It is used in a solution of 1:20 for cleansing suppurating wounds, sinuses, and abscess cavities. *Peroxid of hydrogen* acts through its ability to give off oxygen when brought in contact with organic matter. It is valuable as a mouth-wash where it can come in contact with the superficial tissues. Can be used in solutions of 50 per cent. or less. *Formaldehyd* in the form of a 40 per cent. solution in water, known as "formalin," is one of the most useful of all germicides. It is, however, too irritating to the skin and mucous membranes for general surgical use; its chief value is as a disinfectant. Although very diffusible, formaldehyd has very little penetrating power, and consequently can be considered only as a surface disinfectant. For this purpose it has marked advantages in that, although a powerful germicide, it is comparatively harmless to higher animals, and also has no injurious effect upon cloths or metals. The best method to employ is to mix powdered permanganate of potassium with an equal amount of sand, and to this add formalin. The formaldehyd gas will be given off freely, but there will be no danger of an explosion, as may occur if the sand is omitted. The room to be disinfected must, of course, be carefully sealed, with the exception of one door, which should be sealed as soon

as the formalin has been added. About 1 quart of formalin should be evaporated for every 1000 cubic feet of room space. Sheets wet with formalin may be hung up in the room as a make-shift substitute for the above.

**Disinfection of the hands** is of the greatest importance when dealing with patients, in order to avoid all possibility of transmitting any disease from one person to another. Ordinary washing with soap and water, although sufficient as a rule, does not get the skin free from bacteria. Probably the most satisfactory method is to wash the hands for ten minutes in as hot water as can be comfortably borne, using a sterilized stiff nail-brush with plenty of soap, then rinse off the soap in clean hot water.

All instruments should be washed and then sterilized by being boiled for ten to fifteen minutes in water containing a small amount (1 to 2 per cent.) of soda (carbonate, bicarbonate, or baborate), in order to prevent rusting. Great care should be taken to have all instruments clean, lest infection should be carried from one person to another. Syphilis has been conveyed by unclean dental instruments.

**Disinfection of Dejecta.**—When possible, all discharges should be destroyed by fire, but this method is limited practically to expectorations and nasal discharges. In diphtheria or in other infectious conditions of the mouth, throat, and nose the discharges should be received in old cloths, paper napkins or paper boxes, and then burnt. The intestinal discharges in typhoid fever should be intimately mixed with a 5 per cent. solution of chlorinated lime, and be allowed to stand for one hour before being disposed of.

**Disinfection of Clothing.**—All fabrics coming in contact with a case of infectious disease must be considered as dangerous until they have been sterilized properly. Such materials can be placed in the wash-boiler and boiled for one-half hour, then hung up out-of-doors to dry exposed to the sun. Outer clothes cannot be treated in such a manner, and should be exposed to hot air at a temperature of 110° C. This is difficult, as no arrangements exist in private houses for carrying out this

method. About the most that can be done is to expose them for some hours to fresh air and sunlight.

**Disinfection of Furniture, Etc.**—In addition to the disinfection of the room with formaldehyd, the floor should be scrubbed (using rubber gloves) with formalin, 5 per cent. carbolic acid solution, or 1:1000 mercuric chlorid solution (no soap should be used with the latter, as it combines with the chlorid solution and prevents its action).

## CHAPTER XIII

### BACTERIOLOGIC METHODS

#### CULTURE-MEDIA

As has already been stated (p. 21), there are certain requirements known as Koch's laws, or postulates, that must be fulfilled in order that we can prove a certain organism to be the cause of a definite pathologic condition. These require, among other things, that the organism be grown outside of the body on artificial culture-media; these to be composed of such substances in such proportion as will enable the bacteria to live and multiply. Inasmuch as the different bacteria vary greatly in their metabolic activities, it becomes necessary to have various kinds of media; there are, however, certain forms that are employed routinely. Such media should contain at least 80 per cent. of water, should be of neutral or feebly alkaline reaction, and of a composition which, for the pathogenic types at least, should closely approximate the juices of the animal body. Such nutritive materials may be either liquid or solid, and some of the most useful may be liquefied and solidified at will.

**Bouillon.**—This medium is used by itself and also as the nutritive basis of certain solid media. It may be made up with lean beef or with 3 gm. of beef extract. If the former is used it must be freed from fat and gristle and finely minced; 500 gm. of it are mixed with 1000 c.c. of water and allowed to stand on ice for twelve hours. At the end of this time the liquor is poured off, that remaining in the meat squeezed through a cloth, and enough water added to bring the amount up to 1000 c.c. It is then filtered, and to the clear filtrate is added 10 gm. of Witte's peptone, 5 gm. of sodium chlorid, and

enough water to bring the quantity up to 1000 c.c. This mixture is boiled until everything is dissolved, and it is then neutralized, as its reaction is very acid.

The neutralization should be very carefully carried out so that the final reaction is slightly alkaline. This is done by carefully adding a 10 per cent. solution of caustic soda and testing with litmus-paper. During this process the solution is kept boiling. After the materials are all dissolved and the solution titrated, it should be allowed to cool before filtering. If filtered while hot there will be a subsequent precipitation of meat-salts, which will cloud it.

*Glucose bouillon* is similar to the above, except that it contains 1 per cent. glucose in addition.

**Agar-agar.**—To 1000 c.c. of beef bouillon 15 gm. of agar-agar are added and boiled for one hour, constantly stirring. Water is added at various intervals to keep up the required volume. After the boiling is done the contents are allowed to cool to 60° C., at which point an egg is beaten into the fluid, which is again boiled for about ten minutes. Then filter while hot through wet filter-paper. A jacketed filter kept warm by a gas flame facilitates the process. As the fluid cools while filtering, it has to be again heated until all passes through. The finished agar should be a colorless, nearly transparent, firm jelly.

The purpose of the agar-agar is to give a medium that will remain solid at a temperature equal to that of the body, which is the best for many bacteria, the agar itself not contributing any nourishment to the medium. The agar will melt at about 42° C., but will again solidify when cooled.

**Gelatin.**—To 1000 c.c. of boiling beef bouillon add 100 gm. of golden seal French gelatin. When the gelatin is thoroughly dissolved boil for about five minutes and neutralize by the method described for bouillon. The mixture is cooled to 60° C., an egg beaten in, boiled about ten minutes, and filtered through wet filter-paper. Sufficient water should be added to bring the quantity up to the original amount. It may have to be reheated a couple of times before filtration is complete. As the gelatin solution is strongly acid in reaction, it must be corrected carefully by titration. Care must be taken not to bring the

mixture to the boiling temperature more frequently than is necessary, as the power of coagulation may be destroyed.

This medium melts at temperatures above 22° C.

*Glucose gelatin* is gelatin that has been dissolved in glucose bouillon.

**Blood-serum** (*Löffler's Mixture*).—The blood-serum is obtained by collecting it at a slaughter-house. Jars holding about 1 gallon should be used. These should be clean and sterile. The collected blood is put aside in a cool place for twenty-four to forty-eight hours until the blood is completely clotted. If the clot adheres to the side of the jar, loosen it with a glass rod. The clear serum is removed with a pipet. This is then mixed with glucose bouillon.

Glucose bouillon (1 per cent.).....	1 part
Beef blood-serum.....	3 parts

The above is then run into test-tubes to a depth of about 4 cm. These are placed on an incline so that they will be on a slant when coagulated. In this position they are placed in a hot-air sterilizer and kept at a temperature between 85° and 90° C. for one hour. The thermostat should be carefully watched so as not to have the heat vary from the above figures. After the medium has become thoroughly coagulated the tubes are sterilized in steam for one-half hour on three successive days. When blood-serum tubes are not available a good substitute in the form of a hard-boiled egg may be used. Remove the egg from the water, and with a sterile instrument remove a part of the shell, leaving the coagulated albumen exposed. Inoculate this surface with the suspected material, cover with a glass, and then place near a stove or in a "Thermos" bottle, and allow to incubate for eighteen to twenty-four hours. The blood-serum is particularly useful in the cultivation of the *Bacillus diphtheriæ*, which grows upon it rapidly and with a characteristic appearance.

**Litmus Milk.**—To milk that has been freed from cream enough of a freshly prepared aqueous solution of litmus is added to give it a blue color. This is run into test-tubes which are treated by intermittent steam sterilization. Fresh milk

should be used and the process quickly carried out to prevent as much as possible the growth of bacteria. This medium is the best for determining the formation of acids or alkalis by bacteria.

**Potato Cultures.**—The potatoes should be thoroughly scrubbed with brush and water. Solid cylinders of a size to fit the test-tubes are cut with a cork-borer. They are then split obliquely and the pieces placed in running water for some twelve hours. The oblique pieces are then placed in test-tubes with the larger end downward. A few drops of water should be added to prevent drying. The tubes are then put through the fractional steam sterilization.

**Dunham's Pepton Solution.**—

Pepton.....	10 gm.
Sodium chlorid.....	5 “
Distilled water.....	1000 c.c.

The pepton and sodium chlorid are dissolved by boiling and the mixture filtered. Test-tubes are filled and sterilized. This solution is commonly employed for the detection of indol.

**Filling of Test-tubes.**—New test-tubes are best cleaned by washing in a very weak solution of nitric acid, then rinsing in water, and allowing to become dry or nearly so. Old tubes that have contained cultures are boiled for nearly one hour in a 6 per cent. solution of common soda.

The cleaned tubes are plugged with *raw* cotton and placed in the hot-air sterilizer at 150° C. until the cotton has turned brownish. This is to mold the stopper to the shape of the tube.

To fill the tubes it is best to take a large funnel and by means of a short piece of rubber connect it to a piece of glass tubing a couple of inches in length. The supply of the medium is controlled by a pinch-cock on the rubber. The glass tube is inserted into the test-tube, the required amount of medium run in, and the cotton plug put back. Care should be taken not to get any of the culture-medium on the neck of the tube, as the cotton would stick to it. If “slant” cultures are to be made, run in about 5 c.c. of fluid; if “stab” cultures, about 8 to

10 c.c. should be used. The filled tubes are then sterilized. After the final sterilization, if "slant" cultures are to be made, the test-tubes are so placed that the medium will come about half-way up the side of the tube.

Instead of test-tubes, flasks of varying sizes may be used to contain the medium.

#### Varieties of Cultures.—

1. Slant.
2. Stab.
3. Petri dish.
4. Esmarch tube.
5. Hanging drop.
6. Anaërobic.

1. *Slant Cultures*.—A platinum wire is taken and heated in the flame. When cool it is inserted into the material to be examined. Then, without touching anything, not even the sides of the tube, the point of the wire is carefully drawn over the surface of the medium and the wire again sterilized. When the cotton plug is removed, the end of the tube should be passed through the flame. Care should be taken at all times that the platinum wire is carefully sterilized before being laid anywhere.

2. *Stab cultures* are made by carefully inserting the platinum wire, which should be straight, into the center of the culture-media. The same precautions as mentioned above should be observed.

3. The *Petri dish* consists of a shallow glass dish with a cover. It is used to a large extent for the purpose of isolating colonies and obtaining pure growths. The tubes inoculated directly from the material examined usually contain several varieties of organisms. The method of *isolating* is as follows: Three tubes of agar-agar or gelatin are melted and then placed in a water-bath at a temperature between 40° and 42° C. A platinum wire with a small loop at the end is inserted into the infected substance and then a tube is inoculated. From this tube a loopful is carried over to tube No. 2, and a third tube is inoculated from the second, the platinum wire being sterilized each time. Three sterile Petri dishes are taken and a tube

is inserted under the cover of one and its contents poured out. This is done with all three, care being taken to have the medium evenly distributed over the bottom of the dish. They are then incubated twenty-four hours at a temperature of  $37^{\circ}$  C.

The first tube will contain so many organisms that Petri dish No. 1 will be covered with colonies. The second tube, being diluted, will give fewer colonies on dish No. 2, while dish No. 3, obtained by pouring out tube No. 3, will have only a few scattered colonies. From this last dish the individual growths may be removed with a sterilized platinum needle and inoculated into a fresh tube, a pure culture thus being obtained.

4. The *Esmarch tube* is made by taking an inoculated tube of melted agar or gelatin, laying it on a block of ice, and rotating till the medium is distributed in a thin coat on the inside. Care must be taken that the contents do not come in contact with the cotton plug. This method has been practically supplanted by the Petri dishes.

5. *Hanging-drop cultures* are obtained by taking a slide in which there is a depression and a ring of vaselin is made around it. A sterilized cover-glass is taken, a drop of bouillon placed on it, and this is inoculated with the usual precautions. The cover-glass is inverted over the depression in the slide and pressed down upon the vaselin. This is put in the incubator for twelve to twenty-four hours and then examined.

6. *Anaërobic cultures* may be obtained in various ways, the essential point being the elimination of free oxygen. A test-tube half full of a medium that will become solid on cooling is boiled, rapidly cooled, and then inoculated by a deep stab. On top of this may be poured melted paraffin, oil, or vaselin to keep out the air. Buchner's method consists in the use of two tubes, a small one to contain the culture, and a larger one to contain a fluid that will absorb the atmospheric oxygen. The solution used consists of pyrogallic acid and sodium hydroxid, about 2 gm. of the former, 20 c.cm. of a 10 per cent. solution of the latter. This is poured into the larger tube, the smaller one placed within it, and it is then tightly corked. A simpler method is one in which a larger tube containing a liquid medium is used. Into this is placed a smaller tube with the closed end

uppermost. During sterilization the air will be displaced, and when the liquid cools the smaller tube will be full of the medium. In this the anaërobic organisms will grow. This method is also of value in determining whether there is any gas formation, and may be used in place of Smith's fermentation tubes.

The oxygen within the container may be replaced by an atmosphere of hydrogen, and the latter tightly sealed.

### EXAMINING BACTERIA

Although the greater part of the examination of micro-organisms is done with stained specimens, yet they should always be examined in the unstained and living condition as well. The best way to do this is by means of the *hanging drop*.

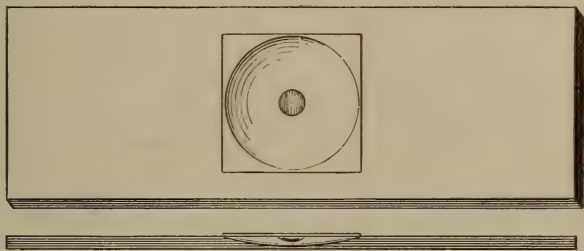


FIG. 80.—THE "HANGING DROP" SEEN FROM ABOVE AND IN PROFILE (McFarland).

In this method a slide with a concavity is used. Around this depression a ring of vaselin is made. A drop of the material to be examined is placed in the center of a clean cover-glass, which is then inverted over the depression in the slide and is pressed down upon the vaselin. Care should be taken that the drop is not large enough to touch the slide. The edge of the drop should be examined, as the central portion is too thick. By this method can be determined the shape, size, grouping, division, sporulation, and motility of the organism.

### STAINING BACTERIA

**Staining Cover-glass Preparations.**—A well-cleaned cover-glass or slide has a small portion of the material for examina-

tion spread out on it in a very thin layer by means of a sterilized platinum wire. The preparation is allowed to dry; it is best not to do it over a flame. When dry the cover-glass is passed rather slowly three times through the flame of a Bunsen burner. This coagulates the albumin and prevents the material being washed off during the process of staining. The cover-glass is covered with the stain and gently warmed for fifteen to twenty seconds over a small flame. The specimen is then washed in water, dried by blotting and by gently warming, and mounted in balsam.

Various of the anilin colors are the ones chiefly used in bacterial staining. They may be used alone or in combination with certain reagents employed to increase the staining power.

Saturated alcoholic solutions of the stains should be kept in stock, and from them the dilute aqueous solutions can be prepared. These latter, however, do not keep well, so various standard preparations are usually kept on hand.

#### **Löffler's Methylene-blue.—**

Sat. alc. sol. methylene-blue.....	30 c.c.
Caustic potash in water (1 : 10,000).....	100 “

This keeps a long time and stains rapidly.

#### **Neisser's Stain for Diphtheria.—**

##### *Solution No. 1*

Methylene-blue.....	0.1 gm.
Alcohol.....	2.0 c.c.
Glacial acetic acid.....	5.0 “
Distilled water.....	95.0 “

Dissolve the methylene-blue in the alcohol and add it to the acetic-acid-water mixture. Filter.

##### *Solution No. 2*

Bismarck brown.....	0.2 gm.
Water (boiling).....	100.0 c.c.

Dissolve the stain in the boiling water. Filter. To stain: Fix the preparation. Pour on the acetic-acid-methylene-blue solution and allow to act from thirty to sixty seconds. Wash. Then pour on the Bismarck-brown solution, and after thirty seconds wash off with water. Dry and mount. The bodies

of the bacilli are brown, with dark blue spots at either end. Best results are obtained with cultures from nine to eighteen hours old.

#### **Carbol-thionin.—**

Sat. sol. thionin in 50 per cent. alcohol.....	10 c.c.
Carbolic acid aq. sol. (2 per cent.).....	100 "

#### **Carbolfuchsin.—**

Sat. alc. sol. fuchsin.....	10 c.c.
Watery sol. carbolic acid (5 per cent.).....	90 "

This stain is very permanent and is useful for many purposes. It is employed in the differential diagnosis of tubercle bacilli. In this method (Ziehl-Nielson) the cover-glass or slide is covered with the above stain and heated until steam rises, for about three minutes. Care must be taken not to boil the stain and to replace the solution as it evaporates. Wash thoroughly in water and then decolorize with about a 10 or 15 per cent. watery solution of nitric acid. Wash again in water, then in 95 per cent. alcohol for thirty seconds, and counter-stain for a minute in Löffler's methylene-blue. The tubercle bacilli will appear as minute red rods; all other organisms will be blue.

#### **Anilin Gentian-violet.—**

Sat. alc. sol. gentian-violet.....	16 c.c.
Anilin water.....	84 "

Anilin water is made by taking:

Anilin oil.....	5 c.c.
Distilled water.....	95 "

Shake thoroughly until a milky fluid is obtained; then filter. This stain should be freshly prepared when needed, as it does not last more than ten days.

#### **Carbol Gentian-violet.—**

Sat. alc. sol. gentian-violet.....	1 c.c.
Aq. sol. carbolic acid (5 per cent.).....	10 "

This solution is permanent, but tends to overstain.

**Gram's Method.**—After the cover-glass has been smeared and fixed it is stained in:

1. Anilin or carbol gentian-violet thirty seconds.
2. Washed in water two or three seconds.
3. Put in Gram's solution, as follows, for thirty seconds:

Iodin.....	1 gm.
Potassium iodid.....	2 c.c.
Water.....	300 "

4. Washed in 95 per cent. alcohol until the color ceases to come out of the preparation.
5. Dry by blotting and in air and mount in balsam.

The value of this method lies in the fact that certain bacteria will retain the stain, while others give it up. In those organisms retaining the stain there has been a combination of mycoprotein, anilin dye, and the iodids that forms a compound insoluble in alcohol. The bacteria stain dark blue or black, while the nuclei are only faintly colored. Nuclei that are undergoing division may stain rather deeply.

An organism is said to stain by Gram's method when it is not decolorized. This power is made use of to differentiate certain organisms that may resemble each other in size and shape.

The more important pathogenic bacteria are divided as follows, according to their reaction to Gram's:

#### STAINED BY GRAM'S METHOD.

Staphylococcus pyogenes.  
 Streptococcus pyogenes.  
 Streptococcus capsulatus.  
 Actinomyces.  
 Bacillus anthracis.  
 Pneumococcus.  
 B. diphtheriæ.  
 B. lepræ.  
 B. tuberculosis.  
 B. tetanus.  
 B. aërogenes capsulatus.

#### DECOLORIZED BY GRAM'S METHOD.

Gonococcus.  
 Bacillus typhosus.  
 B. coli communis.  
 B. of malignant edema.  
 Spirillum of Asiatic cholera.  
 Diplococcus intracellularis meningitidis.  
 B. pyocyaneus.  
 B. of influenza.  
 B. of dysentery.  
 B. of bubonic plague.  
 B. of glanders.  
 Spirochæta of relapsing fever.

## METHODS FOR STAINING SPORES

Spores are the resting forms of various organisms and are stained with difficulty, but when once stained are hard to decolorize.

**Abbott's Method.**—

1. Stain the cover-glass deeply with methylene-blue, heating until the solution boils.
2. Wash in water.
3. Wash in 95 per cent. alcohol, containing 0.2 to 0.3 per cent. HCl.
4. Wash in water.
5. Stain for eight to ten seconds in anilin-fuchsin solution.
6. Wash in water, dry, and mount.

The spores are stained blue; the bodies of the bacteria, red.

**Möller's Method.**—

1. Wash the cover-glass for two minutes in chloroform.
2. Wash in water.
3. Place in a 5 per cent. watery solution of chromic acid for one-half to two minutes.
4. Wash in water.
5. Stain with carbolfuchsin for one minute, heating the solution slowly until it boils.
6. Thoroughly decolorize in a 5 per cent. solution of sulphuric acid.
7. Wash in water.
8. Stain in aqueous methylene-blue (1 gm. to 100 c.c.) for thirty seconds.
9. Wash in water, dry, and mount.

The spores will be red; the bacteria, blue.

The most satisfactory spore-staining method is really the negative staining of the spore obtained when a bacterial preparation is stained by dilute carbolfuchsin or Löffler's methylene-blue. The spore appears as a highly refractile piece of glass in a colored frame. The acid-fast method, as for tubercle bacilli, gives good results, but the decolorizing must be lightly done, otherwise the spore will lose its red stain.

## STAINING OF FLAGELLA

**Löffler's Method.**—

1. Flood the cover-glass with the following solution, which should be filtered before using:

Aqueous solution of tannic acid (20 per cent.).....	10 c.c.
Cold saturated solution of ferrous sulphate.....	5 "
Saturated aqueous or alcoholic solution of gentian-violet or fuchsin.....	1 "

This is very gently heated, not boiled, for about one minute.

2. Wash in water.
3. Stain in anilin gentian-violet or anilin-fuchsin with gentle heating thirty to sixty seconds.
4. Wash, dry, and mount.

**Bowhill's Method.**—Stain the cover-glass in the following solution, heating gently for ten to fifteen minutes:

Saturated alcoholic solution of orcein.....	15 c.c.
Aqueous solution of tannin (20 : 80).....	10 "
Distilled water.....	30 "

Filter the mixture before using. The orcein stain should be at least nearly two weeks old.

In **staining sections** for bacteria Gram's method or that used for the tubercle bacillus is generally employed. Better results are obtained with paraffin sections, but celloidin may be used.

**Staining Capsules.**—

1. Cover the preparation with glacial acetic acid for a few seconds.
2. Drain off (do not wash) and replace with anilin gentian-violet. Pour this off and add more stain until all of the acid has been removed.
3. Wash in a 2 per cent. solution of sodium chlorid and examine in the same.

## CHAPTER XIV

### SPECIFIC MICRO-ORGANISMS

#### ORGANISMS OF SUPPURATION

INASMUCH as suppuration, the formation of a purulent exudate, is so common in connection with the majority of wounds, it seems advisable to start with this subject. Although the great majority of bacterial proteins will cause the formation of pus, there are certain bacteria which are usually found in these discharges; they are the micrococci.

**Staphylococcus Pyogenes Aureus, Albus, and Citreus.**—These three forms of micro-organisms are similar in all their biologic properties, except that they produce different colors in their growth on artificial media. Many regard these as three races of the same species, probably a correct view.

These pyogenic staphylococci are distributed very widely in nature, being found in dust, on the skin and mucous membranes, under the finger-nails, in the alimentary canal, and constantly in the mouth. Fortunately, in the great majority of cases the staphylococci isolated from the above sources are either very slightly virulent or totally avirulent.

*Pathogenesis.*—As a rule, when infection occurs by these organisms the lesion is superficial and circumscribed, as abscesses, boils, and carbuncles, but deep-seated and widespread infections may result. They may enter the blood-stream and give rise to a purulent infection known as pyemia or to an ulcerative endocarditis. They are found also in the lesions of suppurative pleurisy, pericarditis and peritonitis, and play an important part in secondary infections. The staphylococci are associated frequently with the tubercle bacillus in pleurisy and suppurative meningitis, with the pneumococcus in pneumonia, and with the diphtheria bacillus in diphtheria. Osteomyelitis

may result from these organisms. In the human being boils and abscesses have been produced experimentally by rubbing cultures into the skin. In rabbits all forms of purulent inflammation have been produced by inoculating staphylococci into various parts of the body.

*Immunity.*—As yet no marked degree of immunity has been produced by the injection of antisera or of cultures—living or dead. As the staphylococci form very little extracellular toxin, an antitoxic serum of any degree of strength cannot be obtained. Very good results in the treatment of staphylococcal infections have been obtained by the injection of bacterial

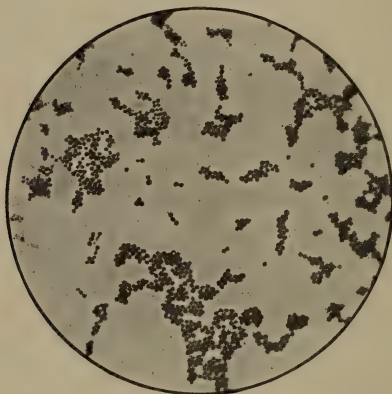


FIG. 81.—*STAPHYLOCOCCUS AUREUS*. FUCHSIN;  $\times 1000$  (Günther).

suspensions of the same strain of coccus as caused the lesion. In this way the resistance of the individual is increased, and cases of acne and furunculosis have recovered rapidly when so treated.

The *Staphylococcus pyogenes aureus* is the most important one of the group from a pathologic point of view, and may be used as the type. It is a non-motile, non-flagellate, non-sporogenous, liquefying, chromogenic, pathogenic, aerobic, and optionally anaerobic coccus, staining by the ordinary methods and by Gram's. It will grow at any temperature between  $10^{\circ}$  and  $44^{\circ}$  C., but the optimum temperature is from  $35^{\circ}$  to  $37^{\circ}$  C.

Pigment production is most marked when grown between 20° and 25° C. in the presence of oxygen. In cultures it produces fatty acids from sugars, forms indol, and is able to liquefy gelatin by the elaboration of ferments (diastases). It will coagulate milk and then gradually digest the casein. In cultures there is formed also a substance, leukocidin, which is destructive to white blood-cells, and one other that acts as a hemolysin.

*Cultures.*—On *gelatin* plates this staphylococcus forms small orange-colored colonies which cause a surface liquefaction. The orange pigment is best seen in the center of the colony. In gelatin stabs it grows as a fine white line, developing its pigment in about three days. It liquefies the gelatin and forms an orange-colored precipitate. On *agar* there is considerable variation in color; is rarely golden, commonly being yellow or cream color. The colonies are moist, shining, and circumscribed. In *bouillon* the growth gives a diffuse cloudiness with a small amount of slightly yellowish sediment. In *milk* the growth causes an acid reaction, with coagulation and final digestion of the casein. On *potato* the most intense color is produced, the growth forming a more or less bright yellow, thick layer.

**Staphylococcus pyogenes albus** has the same characteristics as the above, except that the growths are always white and the liquefaction of gelatin takes place a little more slowly. It is also less pathogenic.

**Staphylococcus pyogenes citreus**, similar, except that it produces a lemon-yellow pigment.

**Staphylococcus epidermidis albus** is habitually present on and in the deeper layers of the skin, and under certain conditions is able, probably, to cause pus formation. It is thought by many to be the *S. pyogenes albus* in an attenuated form.

**Streptococcus pyogenes** is a non-motile, non-flagellate, non-sporogenous, non-liquefying, non-chromogenic, aërobic, and optionally anaërobic organism, pathogenic for man. It stains by the ordinary methods and by Gram's. It grows in chains of 4 to 20 or more individuals.

*Pathogenesis.*—The streptococci are the primary cause of many inflammatory, suppurative, and septicemic conditions:

puerperal infection, erysipelas, endocarditis, meningitis, peritonitis, salpingitis, otitis, pneumonia, and cellulitis. Infection by this organism seldom remains strictly localized. It is a matter of much interest and importance that recent investigations indicate that acute rheumatism is due probably to this organism. As secondary invaders the streptococci may give rise to serious complications, particularly in scarlet fever.

*Cultures.*—Grows best at 37° C. Does not grow luxuriantly on any culture-media, and must be transplanted frequently.

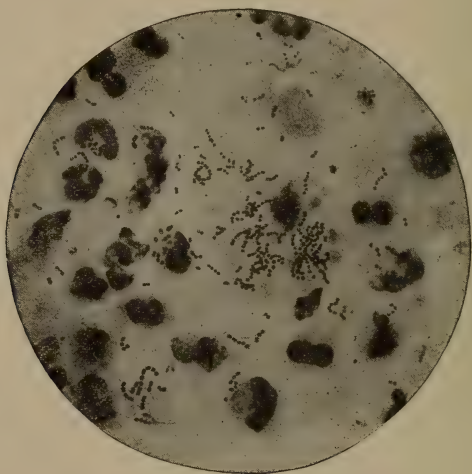


FIG. 82.—STREPTOCOCCUS PYOGENES FROM THE PUS TAKEN FROM AN ABSCESS.  $\times 1000$  (Fränkel and Pfeiffer).

On *gelatin* plates very small, colorless, translucent colonies appear in from twenty-four to forty-eight hours, without any liquefaction of the gelatin. In gelatin stabs a slightly opaque granular line is formed. On *agar* the growth is very delicate and transparent along the line of inoculation. The colonies are small and do not coalesce. In *bouillon* the cocci develop slowly. In *milk* the growth is more luxuriant, with the formation of acid and eventual coagulation; the casein may then undergo digestion. On *potato* there is practically no growth.

*Immunity.*—By the injection of cultures of living virulent streptococci into horses a high degree of immunity has been obtained. This serum is probably both antitoxic and bactericidal in action. Many attempts have been made to cure streptococcic infections by the use of such serum, but the results have not been very satisfactory, no beneficial effect being obtained in many instances. The variations in effects probably are due to there being so many different strains of this organism.

*Coley's fluid* consists of slightly acid bouillon in which a virulent streptococcus has been grown for three weeks, at the end of which time the flask is inoculated with *Bacillus prodigiosus*. After growing for some ten days more at room-temperature, the culture is shaken up, poured into bottles of about 20-c.c. capacity, and rendered sterile by heating to 50° to 60° C. for one hour. The injection of this fluid into sarcoma is claimed to have caused necrosis and eventually a cure of the condition.

In the growth of these bacteria there is formed a toxin that has a marked destructive effect on blood-cells. As killed cultures have a much more marked hemolytic effect than filtered ones, the important product must be an endotoxin.

*Bacillus pyocyaneus* is an actively motile, flagellated, facultative anaërobic bacillus that liquefies gelatin. Is rather short and slender, 0.3 by 1 to 2  $\mu$ . Stains by the ordinary methods, but not by Gram's. It is found in bluish or greenish pus, the color being due to products of its growth.

*Cultures.*—It grows readily on all the ordinary culture-media at room and incubator temperatures. In the presence of oxygen two pigments are formed: the first, *fluorescein*, is a water-soluble green material that soon saturates the media, giving it the characteristic appearance. As the cultures become older a second pigment, *pyocyanin*, blue in color, is formed. On *gelatin* plates the colonies are small, irregular, slightly greenish, and produce a distinct fluorescence of the adjacent gelatin. The gelatin undergoes liquefaction, forming crater-like excavations. Gelatin stab cultures rapidly liquefy along the line of inoculation, with a saucer-like liquefaction at the surface, the medium turning greenish blue. On *agar* the growth develop-

ing along the line of inoculation at first appears bright green. As the culture becomes older the second pigment forms, causing the medium to become a deep blue green or dark blue. In *bouillon* the organism produces a diffuse cloudiness and forms a thin pellicle or scum on the surface. In old cultures the bacteria undergo autolysis and disappear. In *milk* the growth is luxuriant; the casein coagulated and then digested. The

reaction becomes slightly acid for the first day or two, then alkaline. Upon *potato* a luxuriant greenish or brownish, smeary layer is produced.

In addition to the pigments this organism produces a curdling ferment, a fibrin- and casein-dissolving ferment, a gelatin-dissolving ferment, and a bacteriolytic ferment, the so-called pyocyanase. Under favorable conditions it may produce toxins that are fatal to guinea-pigs, the exotoxin

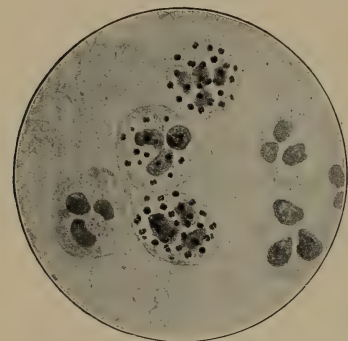


FIG. 83.—GONOCOCCI IN URETHRAL PUS (McFarland).

being more virulent than the endotoxin obtained by lysis of dead bacteria.

**Micrococcus gonorrhœæ**, the *gonococcus*, is a non-motile, non-liquefying coccus found in pairs, with the opposed surfaces slightly concave. It measures from 0.8 to 1.5  $\mu$  in diameter. It is a purely parasitic organism and seems to be pathogenic for man only.

**Pathogenesis.**—In man it gives rise to an acute purulent inflammation of the mucous membranes of the urethra and genito-urinary tract in general, the vagina, uterus, fallopian tubes, and peritoneum. It is also the cause of ophthalmia neonatorum, the acute conjunctivitis of the newborn, and very commonly results in more or less complete blindness. The organisms not infrequently gain entrance into the circulation, causing gonorrheal endocarditis (inflammation of the valves of the heart), pleuritis, and arthritis (inflammation of the joints).

The inflammation may extend from the urethra to the bladder, uterus, and kidneys. The toxic products of the gonococcus appear to be contained within the bodies of the bacteria and disseminated but slightly throughout the culture-media. The gonotoxin seems to be quite stable, not being destroyed by temperatures that are fatal to the cocci. Small quantities of this toxin when introduced into the urethra cause suppuration at the site of inoculation, fever, swelling of the neighboring lymphatic nodes, and muscular and articular pains.

It stains by the ordinary methods, but not by Gram's. The relation of the cocci to the cells is quite characteristic. In most of the inflammatory exudates the gonococci are contained either in epithelial cells or in the leukocytes, very few lying free. This intracellular position is supposed to be the result of active phagocytosis by the cells, of the cocci. An important point in differentiating this diplococcus is that all the others, excepting the meningococcus, retain Gram's stain. This is of particular importance in medicolegal cases.

*Cultures.*—Cultivation is difficult, as the organism does not grow upon any of the ordinary culture-media, and only scantily on any form of artificial medium. The optimum temperature is 37° C., higher temperatures soon causing the growth to cease. The medium that has proved the most satisfactory is composed of ordinary nutrient *agar* to which about one-half the quantity of sterile hydrocele or ascitic fluid is added. On this medium, or on a tube of human *blood-serum*, the cocci in about twenty-four hours form small, isolated, thin, gray colonies that later become confluent and produce a delicate, smeary layer upon the medium. They must be transplanted every few days to fresh tubes, and even then soon lose their power of growth and cease to live.

Attempts have been made to produce an artificial immunity, but as one infection does not confer immunity against further infection the results have not been successful.

**Diplococcus pneumoniae**, or *pneumococcus*, is a minute, slightly lancet-shaped, non-motile, non-liquefying, optionally anaërobic diplococcus. It usually occurs in pairs, but short chains of from four to six may be found. In the tissues and in

sputum there is usually a distinct capsule present. This is not present, as a rule, when grown on artificial media, with the exception of blood-serum.

*Pathogenesis.*—This organism is the cause of lobar or croupous pneumonia, and is found in the lesions of that disease. That true pneumonia can be produced artificially has been proved by experiments made upon dogs, in which pure cultures of the

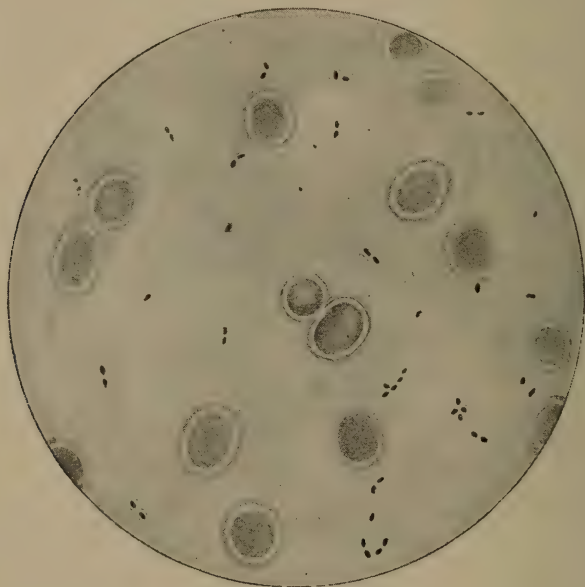


FIG. 84.—CAPSULATED PNEUMOCOCCI IN BLOOD FROM THE HEART OF A RABBIT; CARBOL-FUCHSIN, PARTLY DECOLORIZED.  $\times 1000$  (McFarland).

pneumococcus were injected into a bronchus. In addition to pneumonia, the diplococcus may cause pleuritis, meningitis, pericarditis, or peritonitis. In the early stages of pneumonia, before the crisis, the cocci may be recovered from the circulation by means of blood-cultures.

“Nothing definite is known about the metabolic toxic products of the pneumococcus. That the symptoms of pneumonia

are not entirely dependent upon the disturbance of respiration is clearly shown by the fact that the patients suffer from high fever and have marked leukocytosis with enlargement of the spleen. As filtered cultures are scarcely at all toxic, it is evident that the toxin must be purely or almost purely intracellular." This organism is peculiar in that it causes extreme fibrin formation in the accompanying exudates.

Although not found outside of the human body, pneumococci may be found, particularly in the winter months, in the saliva of some 30 per cent. of all people. That they are frequently virulent is evident, as when such saliva is injected into animals it often causes pneumococcic septicemia.

Stains by the ordinary methods and by Gram's.

*Cultures.*—Is killed by short exposure to low temperatures, by direct sunlight, and lives but a short time on ordinary culture-media. May live, however, in dried sputum or pus for several months.

It grows best at 37° C., but has a range from 24° to 42° C. It will grow on all culture-media except potato, but best upon media that contain serum or hemoglobin. When grown in the presence of red blood-corpuscles there is no hemolysis such as is caused by the streptococci, and the colonies are greenish. On *gelatin* plates (15 per cent. gelatin) the colonies are small, round, circumscribed, finely granular white points which grow slowly, never attain any considerable size, and do not liquefy the gelatin. On *agar* the growth is slight and almost invisible; is more luxuriant if glycerin is present. In *bouillon* the organisms grow well, slightly clouding the medium. On *blood-serum* the growth is quite similar to that on agar.

No immunity results from an attack of this disease; the individual's susceptibility may even be increased. Exposure to cold seems to predispose.

**Bacillus pneumoniæ**, Friedländer's bacillus, is an encapsulated, non-motile, non-sporogenous, aërobic bacillus, short, and with rounded ends. May resemble a coccus. Varies in length, and sometimes occurs in chains of four or more individuals. Stains by the ordinary methods, but is Gram-negative.

*Pathogenesis.*—Although this bacillus is not the usual cause of acute lobar pneumonia, it can give rise to an infection of the lungs that is very severe and often fatal. It can also cause severe purulent inflammations of the serous membranes, pleuritis, pericarditis, meningitis, and peritonitis. It can also cause septicemia in lower animals. It is frequently present in the saliva of many persons and appears to be widely distributed.

This organism appears to be one of a group of bacteria known variously as the *Bacillus lactis aërogenes* and the *B. capsulatus mucosus*.

*Cultures.*—Grows best at body temperature and luxuriantly on all culture-media. In *bouillon* the medium becomes diffusely cloudy, with a pellicle on the surface and a viscid sediment in the bottom. On *gelatin* plates the colonies are round, slightly elevated, shiny, and yellowish white, with no liquefaction of the medium. Upon the surface of *agar* a luxuriant white or brownish-yellow, smeary, viscid, circumscribed growth occurs. *Milk* is not coagulated. On *potato* the growth is luxuriant, quickly covering the entire surface with a thick, yellowish-white layer. On *blood-serum* the growth is similar to that on agar.

**Diplococcus intracellularis meningitidis**, or *meningococcus*, is a minute, non-motile, non-liquefying, non-chromogenic, strict aërobe coccus, usually found in pairs, but may occur in short chains. It very closely resembles the gonococcus in form, is nearly always found within pus-cells, and is decolorized by Gram's stain. Stains by the ordinary methods.

*Pathogenesis.*—Is the cause of epidemic cerebrospinal meningitis, the organisms being present in the pus from the meninges, sputum, and nasal mucus of persons afflicted with the disease. In spinal puncture in this disease the organisms will be found in the pus-cells, and in this way a diagnosis can be made. The bacteria may also be found in the mucous membranes of healthy people, who in this way may be "carriers" of the disease. This organism very closely resembles the gonococcus, but nevertheless belongs to a sharply differentiated species. The meningococcus is pathogenic for mice, while the gonococcus is not. The meningococcus when inoculated into the urethra will not cause an inflammation. Finally, the two organisms can be shown to

be different species by a study of the agglutination and complement fixation reactions. Very favorable results have been obtained in cases of this disease by injecting a serum obtained from animals inoculated with suspensions of meningococci. The serum is used by injecting it into the spinal canal through a lumbar puncture. The precaution must be taken to permit some of the fluid to escape first, and then replace it by the anti-serum, of which not more than 30 c.c. must be injected. This serum must be introduced into the spinal canal so as to come in direct contact with the cocci, as it is antibacterial and not

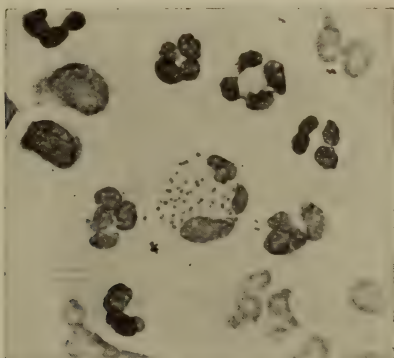


FIG. 85.—MENINGOCOCCUS IN SPINAL FLUID (from Hiss and Zinsser, "Text-Book of Bacteriology," D. Appleton & Co., Publishers).

antitoxic in its action. The meningococcus produces an endotoxin, but no soluble toxin.

*Cultures.*—Grows best at 37° C., but is not easily cultivated. It will grow upon *agar* and *glycerin-agar* and upon Löffler's *blood-serum*. On agar plates the surface colonies consist of an opaque yellowish-brown center, around which a flat, rounded disk spreads out. The cultures must be transplanted frequently.

**Micrococcus catarrhalis** is a coccus commonly found associated with superficial inflammatory conditions of the respiratory tract and conjunctiva. It resembles the pneumococcus, but is Gram-negative. It is readily taken up by the leukocytes,

and may so resemble the gonococcus and the meningococcus that differentiation is difficult. The *M. catarrhalis* may, however, be readily differentiated by the fact that it is easily cultivated, forming large white colonies, irregular in outline. It grows readily on all culture-media at room-temperature, best upon blood agar-agar.

**Micrococcus tetragenus** is a large, round, encapsulated coccus, regularly associated in groups of four—tetrads. It stains by the ordinary methods and is Gram-positive.

*Pathogenesis.*—The organism is pathogenic to mice, but under ordinary conditions does not affect man. The tetrads, however, when present, probably hasten the tissue necrosis in tuberculous cavities, aid in the formation of abscesses of the lung, and contribute to the production of the hectic fever.

*Cultures.*—It grows readily upon artificial media, does not liquefy gelatin.

**Bacillus tetani** is a slightly motile, flagellated, spore-forming, liquefying, obligatory, anaërobic organism. It is found in earth, particularly that which has been manured, and in the discharges from wounds after infection. It is about 0.3 by 2 to 4  $\mu$  in size, usually rod-like, but frequently drum-stick shape on account of the presence of a large round spore situated at the end of the bacillus. It stains by the ordinary methods and is Gram-positive.

*Pathogenesis.*—The most common method of infection is by penetrating wounds made by some instrument, nails, or splinters that have been in contact with infected soil, although the disease may follow superficial and slight injuries. The nearer the wound is to the brain, as on the face or scalp, the more quickly will symptoms develop and the more probable is a fatal result. Inasmuch as the tetanus bacillus is a strict anaërobe, the presence of oxygen will hinder multiplication, but will not destroy the organism. Usually when the injury occurs pyogenic bacteria are present, and these, using up the oxygen, render conditions favorable for the accompanying bacillus. The injury to the tissue cells seems also to play an important rôle, as the *Bacillus tetani* is unable to gain a hold

in normal tissue. The presence of necrotic tissue means the presence of less oxygen, and also interferes with phagocytosis. It has been shown that if the tetanus spores be introduced into the body, after having been washed free from the toxin, they were unable to produce the disease because of the promptness with which the phagocytes took them up. If, however, the toxin was not removed or the body cells injured, the spores would develop into bacilli, form toxin, and produce the disease.

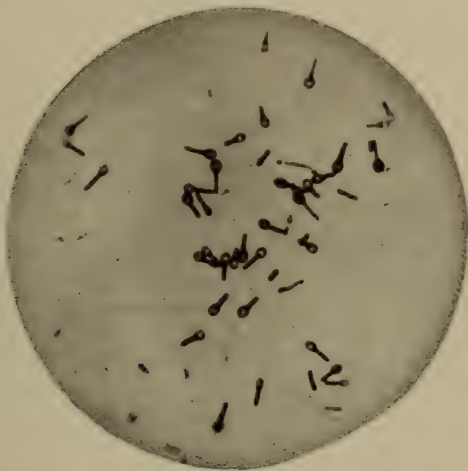


FIG. 86.—BACILLUS OF TETANUS WITH SPORES (Fränkel and Pfeiffer).

When the organisms gain entrance into the body, under favorable conditions, they begin to multiply, form toxin, and in from three to nine days the symptoms will appear. The condition is due not to the presence of the organisms throughout the body, but to the toxin that is conveyed along the motor nerves to the motor areas of the central nervous system, the nerve-fibers and cells undergoing degeneration. Although the chief symptoms are due to nerve disturbances, some of the toxin does get into the circulation. This is shown by the fact that the blood of diseased animals is fatal to susceptible animals; also that the urine is likewise toxic when injected.

The muscles first affected are those that close the jaw, and then those of the back.

*Cultures.*—This organism is cultivated with difficulty, as it will not grow where the slightest amount of free oxygen is present. It grows best at  $37^{\circ}$  C. When conditions are not of the best, spores form. These are very resistant, being able to withstand  $80^{\circ}$  C. for one hour; a temperature of  $100^{\circ}$  C. for one hour being necessary to destroy them. In the growth there are formed various enzymes, one of which slowly liquefies gelatin, another ferments sugar. The most important product of growth is the toxin, which consists largely of tetanospasmin and tetanolysin, both of which are soluble. The first produces convulsions, while the second destroys blood-corpuscles. The toxin is very unstable, being easily destroyed by heat above  $60^{\circ}$  C. It is also quickly destroyed by light, particularly direct sunlight. By some the tetanus toxin is considered to be the most poisonous substance known.

In *bouillon* the medium is clouded, contains a sediment, and forms gas if sugar is present. On *gelatin* plates there is formed a rather dense, opaque central mass surrounded by a more transparent zone, the margins of which consist of a fringe of radially projecting threads of bacilli. At first white, the culture changes to yellow. Liquefaction takes place slowly. In *gelatin* stabs the growth occurs deep in the puncture and is arborescent or tree-like. Liquefaction extends slowly, but may involve the entire mass of gelatin and change it into a grayish-white, syrupy liquid. The growth in *agar* punctures is similar to that in *gelatin* except that there is no liquefaction. In *milk* the organisms grow readily without causing coagulation. Also grow well on *blood-serum*, which is not liquefied.

*Immunity.*—Although an active antitoxin can be obtained by injecting the toxin into animals, it has not proved to be as useful, clinically, as the diphtheria antitoxin. The reason for this has been pointed out by Nocard, who calls attention to the fact that the existence of tetanus cannot be known until a sufficient toxemia to produce spasms exists, and that, therefore, it is impossible to attack the disease in its inception or to begin the treatment until too late to effect a cure. The anti-

toxin, however, has proved to be of immense value as a prophylactic. One of the most frequent causes of tetanus is the infection resulting from injuries due to blank cartridges or fire-crackers, the earth used in them being commonly infected with tetanus organisms. The accepted treatment at present is to lay open such injuries, cleanse them thoroughly, and inject the antitoxin. In this way the neutralization of the toxin can take place as it is formed and the patient be saved. Tetanus following vaccination against small-pox is usually due to infection of the wound, and not to the presence of tetanus spores in the vaccine.

**Bacillus diphtheriæ** is a non-motile, non-liquefying, non-flagellate, non-sporogenous, non-chromogenic aërobic organism from 0.4 to 1.0  $\mu$  broad by 1.5 to 3.5  $\mu$  long, slightly curved, and frequently with clubbed ends. The bacillus is peculiar in its pleomorphism (many forms), for among the well-formed individuals a large number of peculiar organisms are to be found, much larger than normal, some with one end enlarged and club shaped, some greatly elongated, with both ends enlarged. Distinct polar granules may be found at the ends of the bacilli. In addition to the pleomorphism, the variation in staining is characteristic. Some of the bacteria will contain deeply staining granules, others will have stained bands across, while many will stain solidly. With Neisser's method the polar bodies will stain deeply, while the body of the bacillus will be but slightly colored. The ordinary stains may be used, but the most characteristic results are obtained with Löffler's methylene-blue. It also stains by Gram's method.

**Pathogenesis.**—When introduced into the individual this organism, on mucous membranes, causes the formation of a pseudomembrane that consists chiefly of fibrin, but contains desquamated epithelium and the *Bacillus diphtheriæ*. The common site is the upper respiratory tract, particularly the tonsils. The toxin causes a local necrosis, and in that way gains entrance to the body, causing a marked and serious intoxication as a result of its absorption. In addition to the local disturbances there may be marked changes in the important nerves, nerve-centers, and in the parenchymatous cells of the kidneys,

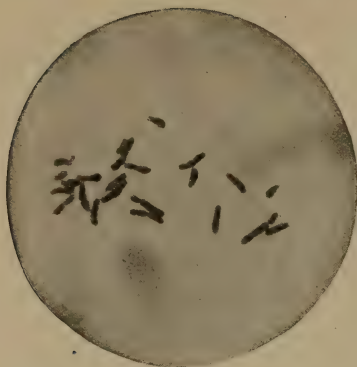


FIG. 87.—*BACILLUS DIPHThERiÆ*,  
FIVE HOURS AT 36° C.

This shows only solid staining forms.

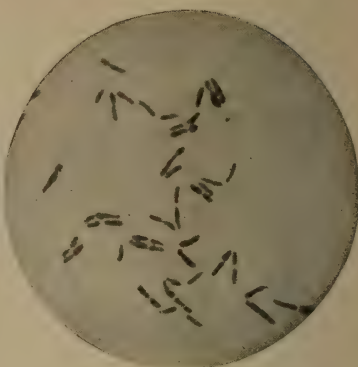


FIG. 88.—*BACILLUS DIPHThERiÆ*,  
SAME CULTURE, EIGHT HOURS  
AT 36° C.

This also shows solid forms,  
many of them with parallel arrange-  
ment.

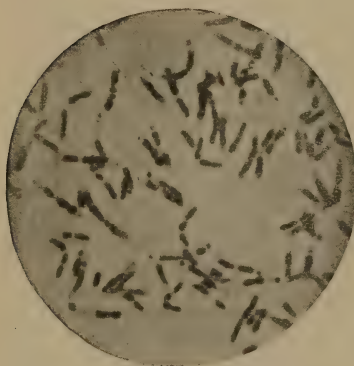


FIG. 89.—*BACILLUS DIPHThERiÆ*,  
SAME CULTURE, TWELVE  
HOURS AT 36° C.

The bacilli stain faintly at their  
ends, and in some small granules are  
seen at the tip of the faintly stained  
portions.

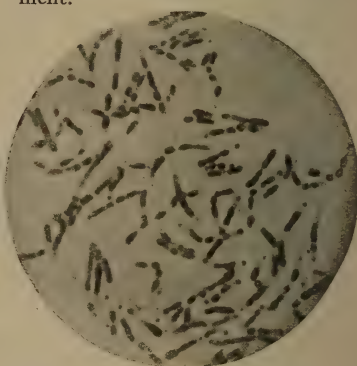


FIG. 90.—*BACILLUS DIPHThERiÆ*,  
SAME CULTURE, FIFTEEN  
HOURS AT 36° C.

The bacilli stain more unevenly and  
the granules are larger.

(Photomicrographs by Mr. Louis Brown. The magnification is the  
same in all— $\times 2000$ . All of the preparations were made from growth on  
blood-serum.) (Francis P. Denny, in "Jour. of Med. Research.")

liver, and heart. Associated with the *Bacillus diphtheriæ* are both staphylococci and streptococci. These may give rise to complications such as endocarditis, pneumonia, and adenitis.

Infection takes place by contact with persons suffering from the disease. It has been found, however, that a convalescent individual may harbor virulent diphtheria organisms for weeks or even months, and in that way be a source of danger to the community.



FIG. 91.—*BACILLUS DIPHThERiÆ*, SAME CULTURE AS FIGS. 87-90, TWENTY-FOUR HOURS AT 36° C.

This shows clubbed and barred forms as well as granular forms. At the lower part of the field is a paired form which shows the characteristic clubbing of the distal ends.



FIG. 92.—*BACILLUS DIPHThERiÆ*, FORTY-EIGHT HOURS AT 36° C.

This is the same bacillus as in Figs. 87-91, but from a culture where the colonies were discrete. It shows long filamentous forms.

(Photomicrographs by Mr. Louis Brown. The magnification is the same in all— $\times 2000$ . All of the preparations were made from growth on blood-serum.) (Francis P. Denny, in "Jour. of Med. Research.")

*Cultures.*—Grows on ordinary media at a temperature of 37° C. Is quite resistant to drying, and has lived on culture-media for eighteen months at room-temperature; also may remain alive in healthy throats for months. Light is detrimental and an exposure of ten minutes to 58° C. kills it.

The best medium is *Löffler's blood-serum*, on which the bacteria form a smooth, smeary, yellowish-white layer at the end of twelve to eighteen hours when grown at a temperature of

37° C. To make a diagnosis of diphtheria a swab of absorbent cotton is brought in contact with the suspected surface and the tube is then inoculated directly. At the end of eight to ten hours there will be a growth sufficient for diagnostic purposes. If blood-serum media cannot be obtained, a hard-boiled egg with the shell removed under aseptic conditions makes a good substitute. The addition of 3 to 5 per cent. of glycerin to the solid media makes them more suitable. On *gelatin* plates the growth is not very good, the colonies appearing as small whitish points. The gelatin is not liquefied. On *agar* or *glycerin-agar* the colonies are slower to develop, but are larger and slightly raised in the center, with a flat surrounding zone that has indented edges. In *bouillon* there is formed a distinct, whitish, granular pellicle which is very brittle. *Milk* is a very good medium. At first alkaline, the reaction becomes acid, but when the culture becomes old the reaction again becomes strongly alkaline.

*Immunity*.—This may be the result of having had the disease, or may be of the passive type obtained by injections of the antitoxin. When the organism grows it produces a powerful toxin, which in favorable cases so stimulates the body cells as to cause the formation of an antibody which is found in the blood. Such a serum is obtained from horses and constitutes the diphtheria antitoxin. This may be used either as a prophylactic or a curative measure. The value of the antitoxin depends upon its use in the early stages, the earlier the better. Of those cases treated with this serum in the first three days of the disease there was a fatality of 8.5 per cent. If injected after the third day there was a fatality of 27.8 per cent. At the outset about 4000 units should be given. In the later stages 8000 to 10,000 units should be injected every four to six hours until the characteristic effect, the freeing of the membrane, is produced. Except in very young children the age should not effect the dosage. In severe cases there should be practically no limit to the amount given, nearly 200,000 units having been used in some instances. Doses of from 600 to 1000 units may be used as a prophylactic in those who have been exposed to diphtheria.

**Bacillus anthracis** is a non-motile, non-chromogenic, sporogenous, liquefying, aerobic bacillus, from 1 to 1.5  $\mu$  in breadth by 5 to 20  $\mu$  in length. It has square ends and is found either singly or in chains or long threads. It stains by the usual methods and by Gram's.

*Pathogenesis.*—This organism is particularly deadly to cattle and sheep, and may give rise to fatal infection in man, when it is known as “malignant pustule.” The bacilli usually enter the body through wounds, giving rise to a local lesion which may give rise to a general bacteremia. When they enter the circulation they multiply very rapidly, and possibly may mechanically overwhelm the animals by absorbing nutriment and oxygen and blocking the capillaries. There is very little toxic action exerted. In men handling wool the spores may be inhaled, giving rise to an infection of the lung.

*Cultures.*—Grows readily on all media; best at 37° C., but has a range of from 14° to 45° C. Between the temperatures of 18° and 41.5° C. spores are formed if free oxygen is present; is most marked at 37° C. At this degree a small refractile point will appear within the protoplasm of the bacilli in the course of a few hours. This increases in size, is oval in shape, and is situated in the center of the bacillus without altering its shape. This is the most resistant form of the organism. The spores can withstand dry heat at 100° C. for one hour, and are highly resistant to chemicals, light, and drying.

On *gelatin* plates the colonies are very characteristic. They appear first as minute, round, grayish-white dots, which spread out into flat, irregular, transparent tufts like curled wool. From a tangled center large numbers of curls, made up of parallel threads of bacilli, extend upon the gelatin. As soon as the colony attains to any considerable size, liquefaction becomes rapid. In gelatin stabs the bacilli grow along the entire track of the wire, but develop best at the surface, where oxygen is plentiful. From the deeper growth fine filaments extend into the surrounding medium. On the surface there soon appears a cup-shaped area of liquefaction; this progresses downward until, finally, the entire gelatin becomes fluid. On *agar* after incubation for twenty-four hours a whitish streak appears;

this rapidly thickens, becomes rather dry and friable, and has lightly notched borders. It is not very characteristic. In *bouillon* a thick, felt-like pellicle forms, from which extensions descend into the clear bouillon below. In the course of time the growth ceases and the pellicle sinks to the bottom of the tube. In *milk* the organisms grow well, causing coagulation to take place toward the third or fourth day. The coagulum is redissolved about the end of the week, the reaction, which is acid, not being changed. Upon *potato* there appears after the second day a whitish deposit, which rapidly thickens and assumes a dull-white color, becoming brown on keeping.

*Immunity*.—It is doubtful if the anthrax bacillus in its growth produces any important toxic substance. An animal that has recovered from an attack, however, is immune, and it is possible to immunize animals by means of vaccines. These are prepared by growing the bacillus at  $42.5^{\circ}\text{C}$ ., at which point spores are not formed. The virulence of the organism soon diminishes until it is harmless to guinea-pigs and rabbits. If this attenuated culture be inoculated into a sheep the animal suffers from a very mild attack of anthrax, and, after it has recovered, it will be found to be capable of resisting the inoculation of a fully virulent organism.

*Bacillus oedematis maligni* is a motile, flagellated, anaërobic, liquefying, non-chromogenic, sporogenous bacillus,  $0.8$  to  $1\ \mu$  in breadth and  $2$  to  $10\ \mu$  in length, with rounded ends. Stains by the ordinary methods, but is Gram-negative.

*Pathogenesis*.—When introduced beneath the skin the bacillus is pathogenic for a large number of animals; cases have been reported in man with usually a fatal result. In order that infection should take place the organisms must be deep within the tissues so as to be protected from oxygen. The bacteria will be found mainly in the subcutaneous tissue and not in the blood.

*Cultures*.—The organism is a strict anaërobe, but under such conditions grows freely at room or incubator temperature in most culture-media. On *gelatin* plates the colonies appear as small shining bodies with liquid, grayish-white contents. Under the microscope they appear filled with a tangled mass of long

filaments. In *glucose-gelatin* stabs a globular area of liquefaction occurs, and marked gas production takes place. In *bouillon* a diffuse clouding appears, followed by the formation of a sediment. There is no surface growth. *Milk* is slowly coagulated. It also grows well upon the surface of *agar*, *potato*, and *blood-serum* when all free oxygen is absent.

**Bacillus aërogenes capsulatus** is a large non-motile, non-flagellate, non-chromogenic, sporogenous, purely anaërobic bacillus,  $0.5\ \mu$  broad by 3 to  $5\ \mu$  long, and with slightly rounded or square ends. It occurs in groups, pairs, or in chains, but is more slender than the anthrax bacillus.

It stains by the ordinary methods and by Gram's.

*Pathogenesis*.—The organism is found in the tissues in the necrotic areas. The disease-producing powers of this organism are distinctly limited, and although it may cause death, it appears to do so only when the affected individual is already debilitated. Being anaërobic, the bacillus cannot live in the circulating blood, but can grow in old clots and in cavities, such as the uterus, where little oxygen can enter. When it enters the body it causes an emphysematous destruction of the tissues before death, and the formation of a large amount of gas postmortem. After death has occurred the bacilli are no longer inhibited by oxygen in the blood, so there is much gas formed.

*Cultures*.—Usually in the body-fluids and often in cultures the bacilli are surrounded by distinct capsules—clear, unstained zones. It grows on the ordinary media, but in *glucose-gelatin* shows best the characteristic gas production. Does not cause liquefaction, but the gelatin becomes softer. In deep stab cultures it produces small knot-like, grayish-white colonies from which extend fine hair-like or feathery projections. In *agar* the deeper colonies grow best and produce so much gas that the medium may be pushed to the top of the tube. In *bouillon* the growth is rapid, the medium becomes cloudy, and a frothy upper layer forms. After a few days the bacilli fall to the bottom of the tube, leaving the bouillon clear. The reaction becomes strongly acid. In *glucose bouillon* the growth and gas formation is more luxuriant. In *milk* the growth is rapid and

luxuriant, coagulation occurring in from twenty-four to forty-eight hours. On *potato* there is a thin, moist, and grayish-white growth, with bubbles in the fluid at the bottom and sides of the tubes. As this bacillus is strictly anaërobic, the above growths will not take place unless all free oxygen has been removed.

**Bacillus influenzae** is a minute, non-motile, non-liquefying, non-chromogenic, aërobic bacillus. Is very small, about 0.2 by 0.5  $\mu$ , usually found singly, but at times occurring in chains of three to four.

Stains by the ordinary methods, but is Gram-negative.

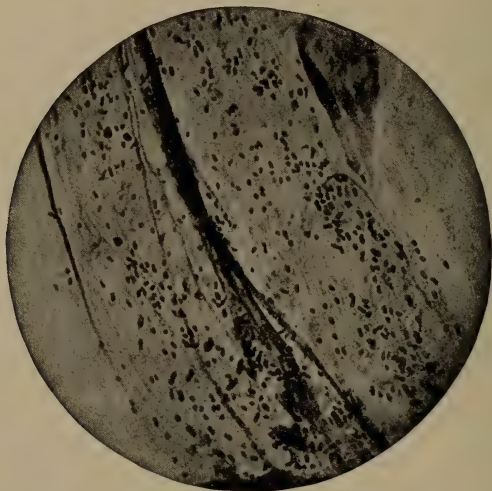


FIG. 93.—BACILLUS OF INFLUENZA. SMEAR FROM SPUTUM (after Heim).

**Pathogenesis.**—The organism is found in the discharges from the nose and from the bronchi of those having the disease. It has also been found in the blood. Although pathogenic for few laboratory animals, this organism can cause many manifestations in the human being. Commonly causing bronchitis, and pneumonia, both croupous and catarrhal, it can give rise to abscess formation, particularly of the middle ear, with mastoiditis and meningitis. It may complicate true pneu-

monias and thus seriously affect both old and young. In some cases it apparently gives rise to intestinal disturbances. On account of the marked general depression that accompanies infection it would seem that the organism must produce a powerful toxin. No immunity appears to result from infection, the individual, indeed, seemingly becomes more susceptible.

*Cultures.*—Is easily destroyed by light, drying, and heat;  $60^{\circ}$  C. for five minutes will kill. Grows best at  $37^{\circ}$  C. and is strictly aërobic. Grows very poorly on artificial culture-media, but develops best on media smeared with blood. After twenty-four hours the colonies appear as minute, colorless bodies,

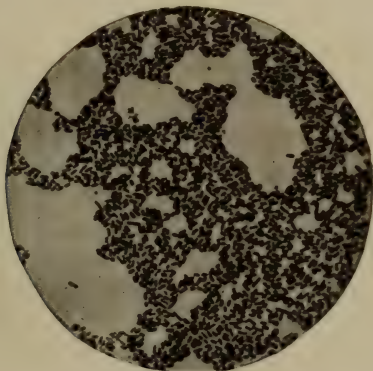


FIG. 94.—BACILLUS TYPHOSUS, FROM A TWENTY-FOUR-HOUR-OLD AGAR-AGAR CULTURE.  $\times 650$  (Heim).

looking like dewdrops, but not coalescing. When grown together with the *Staphylococcus aureus* the colonies of the bacillus grow to an unusually large size within twenty-four hours. This peculiarity seems to depend upon the action of certain substances secreted by the staphylococci or to some change induced in the medium as a result of their growth.

*Bacillus typhosus* (Koch-Eberth bacillus) is a motile, flagellated, non-sporogenous, non-liquefying, non-chromogenic, aërobic, and facultative anaërobic bacillus,  $0.5$  to  $0.8 \mu$  broad by  $1$  to  $3 \mu$  long, with rounded ends. Seldom occurring in chains.

Is stained by the ordinary methods, but is Gram-negative.

*Pathogenesis.*—This organism is the cause of typhoid fever. Any doubt has been removed by the fact that the introduction of the dead organisms protects the individual from attacks of the fever. Outside of the body it is found in fluids, water and milk, that have been contaminated by discharges from infected persons. It is found in the urine and feces of patients, as well as in the blood, tissue lesions, and the gall-bladder. In this latter place the organisms may remain for many years (ten to thirty) after the patient has recovered from the attack. The infected person is evidently immune, but, as a “typhoid carrier,” may be the source of infection to many others.

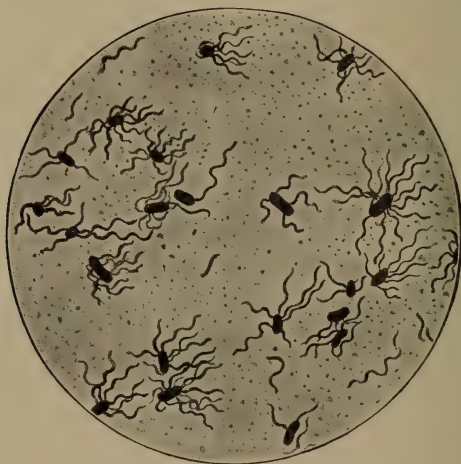


FIG. 95.—*BACILLUS TYPHOSUS*, SHOWING FLAGELLA (McFarland).

*Cultures.*—Grows upon all ordinary media at body temperature. Is readily destroyed by heat,  $60^{\circ}$  C. for ten to fifteen minutes killing it. It can, however, withstand long exposure to cold, remaining alive in ice for several months. In distilled water it may live for some months, provided no saprophytic organisms are present, in which case the typhoid bacilli soon die. Drying and exposure to sunlight soon kill.

On account of the very close resemblance to the *Bacillus coli communis* much work has been done in devising methods by

which the two can be distinguished. On *agar* the colonies are not characteristic, being round, grayish white, and shining. In *bouillon* the only change produced is a diffuse cloudiness.

The following are the chief differences between the two:

	B. TYPHOSUS.	B. COLI COMMUNIS.
Colonies on gelatin plates:	On surface large, thin, and bluish, with notched border; yellowish brown in center. Deep colonies, brownish yellow and sharply circumscribed. Non-liquefying. Develop more slowly.	On surface large, yellow-brown, round or oval, with irregular border. Deep colonies, round, yellowish brown, homogeneous. Non-liquefying.
On potato:	Usually forms a thick, moist, and shiny invisible film. Sometimes yellowish or brownish.	Luxuriant growth. Yellowish brown and glistening.
Milk:	Slightly acidulated, but not coagulated. Diffuse cloudiness.	Rapid coagulating and marked acidulation. Turns blue litmus milk red, colors entire medium. Marked turbidity.
Peptone media:	No indol formation.	Indol formed within twenty-four to forty-eight hours.
Ferments:	No gas formed in media containing sugar.	Fermentation whenever sugar is present.
Potassium nitrate:	Not reduced.	Reduced to nitrites and then to ammonia.
Conradi-Drigalski medium:	Blue, transparent colonies.	Red, opaque colonies.
Endo agar:	Colorless colonies.	Red colonies.
Neutral red:	Color remains red.	Changes to yellow.
Agglutination test,	Typhoid bacilli are clumped when acted upon by diluted serum from the blood of typhoid patients.	No clumping.
Widal reaction:		

*Immunity.*—Following an attack of typhoid fever the individual is usually immune from further attacks for a long time. Excellent results in giving rise to an artificial immunity have been obtained by the injection of typhoid bacterins—solutions containing more or less definite amounts of killed typhoid bacilli. This method has been employed mainly in the armies through-

out the world, and has, in many instances, apparently eliminated this disease.

As a result of infection by this organism there appears, at the end of from five to seven days, a substance in the blood-serum known as an agglutinin. An important test in the making of a diagnosis of typhoid fever, known as the Widal reaction, is based upon the principle that when the serum of a patient suffering from typhoid fever is added to a fresh culture of the typhoid organism, the bacilli will gather into clusters and gradually lose their motility, a process known as clumping.

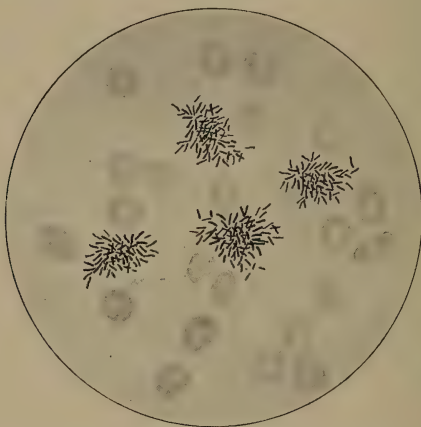


FIG. 96.—AGGLUTINATION OF THE TYPHOID BACILLUS BY A SPECIFIC SERUM.

The reaction is performed as follows: The most satisfactory way is to obtain the blood in a fresh state, and if one can get a sufficient amount to allow of the use of the serum alone, it is even better. A drop of blood or serum is forced out of a capillary tube, in which it should be obtained, and to this 9 drops of sterile water are added. This is thoroughly mixed, and 1 drop of this mixture added to 1 of the culture gives a dilution of 1 : 20. It is generally recommended to use a bouillon culture not more than twenty-four hours old. Some authors recommend an agar culture, but there may be some difficulty

in breaking up the masses of bacilli. Dilutions of 1 : 10 and 1 : 50 also should be employed as control tests. The reason for diluting is that in the pure serum there may be substances that will cause agglutination for many bacteria, and, therefore, is not specific. A drop of the diluted serum and culture is placed on a cover-glass, which is then inverted over a hollow-ground slide. The cover should be held on with a ring of vaselin so as to prevent evaporation. The reaction is said to be positive if, within forty-five minutes, the bacilli are found to be gathered in little groups and their motility almost or entirely absent.

If the blood cannot be sent in the fluid state, several drops of blood should be placed on a clean slide and, when dry, sent to the laboratory. One of the drops of blood is dissolved in a drop of sterile water, and then diluted until the proportion is approximately 1 : 500.

Although this reaction usually appears within a week after the onset of the disease, it may be delayed until much later. It may be present as a result of a previous attack of typhoid fever, so one must be on guard lest a mistaken diagnosis be made.

**Paratyphoid Bacillus.**—Under this heading are described certain organisms which in many respects resemble the typhoid and the colon bacilli. They are all Gram-negative motile bacilli which do not form spores or liquefy gelatin. Infection by them gives rise to a condition similar to typhoid fever, except that the clinical symptoms are usually much milder, and the intestinal lesions may be absent. The two chief varieties are the Paratyphoid A and the Paratyphoid B.

**Bacillus Coli Communis.**—In its general characteristics it resembles the *B. typhosus*, and can be distinguished from the latter only by careful cultivation on special media. (See p. 235, under *Bacillus typhosus*.)

Is stained by the ordinary methods, but is Gram-negative.

**Pathogenesis.**—Normally, this organism is found in the feces of all animals, and in water that has been contaminated by them. In man it may act in a secondary rôle, but there are cases of appendicitis, peritonitis, and cystitis in which the colon bacillus

appears to have been the exciting agent. Suppurative inflammation of the bile-ducts has also been caused by it. It may give rise to terminal infections, those occurring shortly before death, and almost immediately after death it begins to penetrate the intestines, and is the most frequent contaminating micro-organism met with in cultures made at autopsy.

*Immunity*.—It has been shown that the colon bacillus contains a toxin within the cell which under ordinary conditions does not diffuse from it into the culture-medium. When injected repeatedly into animals it gives rise to the formation of agglutinins within their blood. As yet no antisera have been obtained that are of any value in colon infections, but much benefit has resulted from the use of bacterins.

*Bacillus pestis* is a minute, non-motile, non-flagellated, non-sporogenous, non-chromogenic, non-liquefying, aërobic bacillus. Is very short, 1.7 by 2  $\mu$ , with rounded ends. Varies greatly in shape.

Is stained by the ordinary methods, but is Gram-negative. The rounded ends stain more deeply than the middle, thus frequently giving an appearance of a diplococcus.

*Pathogenesis*.—This organism is highly pathogenic for man, giving rise to the bubonic plague. Investigations would indicate that the disease begins in rats. When an infected rat dies the fleas leave it and pass on to other rats or else human beings. They then bite their host, and when so doing deposit fecal material on the skin. Plague bacilli are in these discharges, and as a result of rubbing the bite gain entrance into the person. From the localized injury the infection spreads to the adjacent lymph-nodes, with the formation of buboes (enlarged suppurating lymph-nodes). General bacteremia with death commonly ensues. Sometimes, instead of skin infections, the bacilli may get into the lungs, causing pneumonic plague, the most fatal type. The bacilli will be present in the sputum. Practically all domestic animals are susceptible, particularly the rodents, as rats and squirrels.

*Cultures*.—Grows well on artificial media at a temperature of 37° C. Is easily destroyed by heat, 55° to 60° C. for about ten minutes, exposure to sunlight for three to four hours, and

weak antiseptic solutions soon destroy. In dried pus the organism is more resistant, and may retain both its vitality and virulence for several weeks. In soil the bacillus remains alive for several months. In *bouillon* a more or less marked turbidity appears, and occasionally a pellicle is formed on the surface. If there is complete freedom from vibration, a typical stalactite growth will take place. On *agar* the bacilli grow freely in the form of transparent white colonies which cannot be distinguished from the colon group. On *gelatin*, rounded, granular, and yellowish colonies form, but they do not cause liquefaction. In stab cultures a yellowish, semitransparent growth forms on the surface, while a whitish streak marks the line of the stab. In *milk* the growth is poor and the medium is not coagulated. On *potato* the growth is slow and slight, consisting of a whitish or yellowish streak.

*Immunity*.—Larger animals—as horses—have been immunized. Their serum contains specific agglutinins and bacteriolysins as well as an antitoxin, and is capable not only of preventing the disease, but also of curing it in mice and guinea-pigs, and probably in man. Haffkine, by injecting a bouillon culture that has been killed by exposure to 70° C. for one hour, has been very successful in protecting people against the plague. The immunity so obtained lasts about a month.

**Bacillus of Bordet-Gengou** is the organism that experimentally has been proved to be the cause of whooping-cough. It occurs as very minute oval rods of about the same size as the influenza bacillus, 0.3 by 1.5  $\mu$ . Is somewhat pleomorphic. Is non-motile, non-sporogenous, and very difficult to cultivate primarily, but by subcultures growth can easily be obtained on ascitic agar, serum-broth, and blood-broth. Is a strict aërobe.

The organisms do not stain readily and are Gram-negative.

**Bacillus of Koch-Weeks** is the organism of acute contagious conjunctivitis ("pink eye"). Is a minute, slender bacillus, non-motile, non-flagellated, non-sporogenous, non-liquefying, non-chromogenic, aërobic, and optionally anaërobic. Stains by the ordinary methods, but is Gram-negative. Measures 1 to 2 by 0.5  $\mu$ .

In man a trace of a culture smeared on the conjunctiva gives rise to an acute conjunctivitis.

The organism is aërobic and fails to grow, or grows very feebly, on the ordinary media, but on media containing blood or serum gives rise to a good growth at a temperature of 37° C.

**Bacillus Dysenteriae (Shiga).**—A non-motile, non-flagellated, non-sporogenous, non-liquefying, non-chromogenic, aërobic, and optionally anaërobic bacillus.

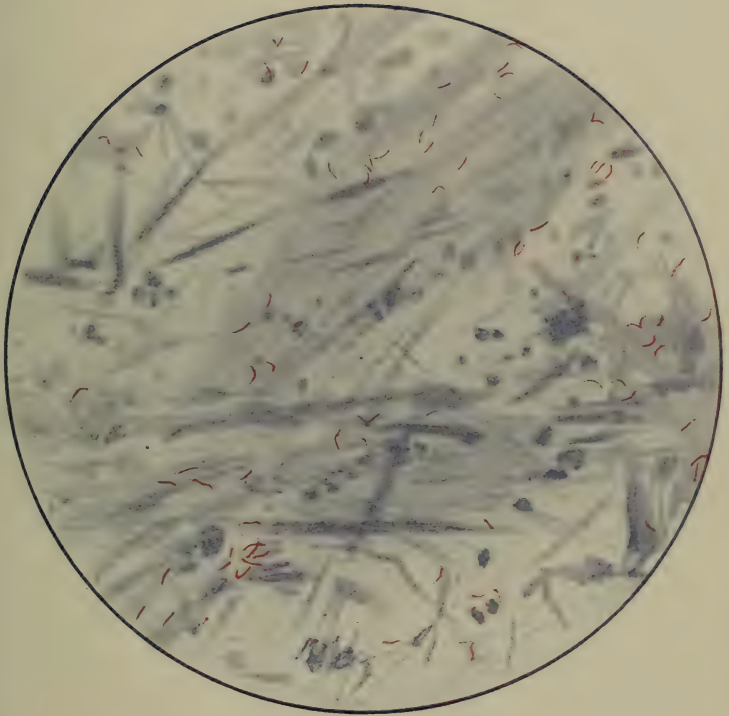
Stains by the ordinary methods, but is Gram-negative.

**Pathogenesis.**—Shiga has come to the conclusion that the *Bacillus dysenteriae* is the specific cause of the epidemic dysentery common in Japan. Since then a similar organism has been found in epidemics in the United States. This bacillus seems to play an important part in the summer diarrheas of children, and has been isolated from the stools in such cases. It is also pathogenic for young cats, dogs, and guinea-pigs.

**Cultures.**—Grows well on alkaline media at a temperature of 37° C. On *gelatin plates* the colonies are small and like dew-drops, with no liquefaction. In *gelatin punctures* the growth consists of crowded, rounded colonies along the line of inoculation, with a grayish-white growth upon the surface. Quite closely resembles the growth of the typhoid bacillus. On *agar* large solitary colonies develop at the end of twenty-four hours. They are bluish white and rounded. In *milk* there is at first slight acid formation, then the medium becomes alkaline, but no coagulation takes place. On *potato* the growth is like that of the typhoid bacillus, but at the end of twenty-four hours becomes yellowish brown. In *bouillon* there is a diffuse growth after twenty-four hours. This gradually sediments until the upper part of the tube is clear. No pellicle is formed. In *peptone solution* no indol is formed.

**Bacillus tuberculosis** is non-motile, non-flagellate, non-sporogenous, non-liquefying, non-chromogenic, non-aërogenic, distinctly aërobic, and acid resisting. It commonly occurs in the form of slender, slightly curved rods with rounded ends, not infrequently showing branches. For this reason it may not be a bacillus, but an organism belonging to the higher bacteria. It measures from 1.5 to 3.5  $\mu$  by 0.2 to 0.5  $\mu$ .

PLATE I



TUBERCLE BACILLI FROM SPECIMEN OF SPUTUM. (From Bonney, "Pulmonary Tuberculosis.")

Bacilli red, other organisms and tissues blue. The so-called attenuated variety of tubercle bacilli. Note the elongated rods, some of which are notched and beaded. Note also faintness and irregularity of stain.



*Staining.*—This bacillus belongs to a group of organisms known as “acid fast,” on account of their ability to resist decolorization by acids. The tubercle bacillus is very difficult to stain, and special methods have to be employed. This resistance to staining is probably due to a surrounding capsule that consists of a fatty or waxy substance, inasmuch as it can be colored by the fat stains, such as Sudan III. Under some conditions this bacillus may not possess its acid-fast properties, yet when inoculated into animals the same organisms will produce tuberculosis, and acid-fast bacteria will be found.

The following method, that of Ziehl-Nielson, is commonly employed for staining tubercle bacilli, particularly in sputum. After having made, dried, and fixed the smear, the cover-glass or slide is covered with carbolfuchsin (saturated alcoholic solution of fuchsin 10 c.c., 5 per cent. watery solution of carbolic acid 90 c.c.) and carefully heated, until steam rises, for some three or more minutes. Care must be taken not to boil the stain and to replace the solution as it evaporates. Then wash the smear thoroughly in water and decolorize with about a 10 to 15 per cent. solution of nitric acid in 95 per cent. alcohol. Will take about thirty seconds to a minute. Wash again in water and counterstain in Löffler’s methylene-blue. Wash and examine. The tubercle bacilli will appear as minute red rods; all other organisms and cells will be blue.

With Gram’s method the bacillus retains the stain.

*Pathogenesis.*—Experiments and investigations carried on all over the world since the time of Koch’s announcement have proved conclusively that this is the organism which gives rise to tuberculosis. There are possibly several types of the organism, but those producing the disease in human beings and in cattle are the two most important. Those causing the disease in birds, reptiles, and fish need not be discussed. The disputed point in question at present is whether or not the bovine type can give rise to human tuberculosis. There has been much argument for and against, but it seems to be proved that human beings can be infected. There are cases on record where tubercles have developed on the hands after performing autopsies on diseased animals. It is quite probable that many of the cases

in children of tuberculosis of the cervical lymph-nodes are due to infection acquired from the use of tuberculous milk. It is also probable that the intestinal tuberculosis of children is due to the bovine type of bacillus in many instances.

*Cultures.*—This bacillus only grows in artificial cultures, provided that the medium contains serum, glycerin, yolk of egg, or fragments of tissue. It is an aërobic organism and grows only at temperatures above  $30^{\circ}$  C. In the case of human tubercle bacilli growth ceases at  $41^{\circ}$  C., and in the case of the bovine-bacilli, at  $44^{\circ}$  to  $45^{\circ}$  C. The optimum temperature is  $38^{\circ}$  C. In order to obtain a pure growth it is best to first inoculate a guinea-pig with the suspected material. In the course of a couple of weeks the lymph-nodes will be enlarged, due to the disease. These should be removed with aseptic precautions, portions carefully taken, and culture-tubes be inoculated. Many tubes should be used, as some will either show no growth or else may be contaminated.

After inoculating *blood-serum* the growth will be apparent to the naked eye after about twelve days in the form of small, white, round, scaly, dry looking colonies scattered over the surface of the medium. On further incubation the colonies become raised, but maintain their scaly appearance, and the margins are irregular in outline. This medium is not very satisfactory and is not much used.

*Glycerin-agar*, except for primary cultures, is the best medium upon which to grow the bacillus, particularly if a little glucose be added. The growth begins as on serum, but the colonies are both larger and more numerous. They rapidly become confluent, and form a thick, whitish, dry, rough, scaly layer. After being subcultivated a few times the growth becomes very abundant, moist, and greasy. When old the growth has a reddish tint. On *bouillon* containing glycerin and glucose the growth takes place in the form of a pellicle, which is dense, creamy white, dry, and very friable. The fluid remains clear, although the pellicle may eventually break in pieces and fall to the bottom of the tube. The organism will grow also on *glycerinized potato* and on Dorsett's *egg-medium*. This latter consists of the whites and yolks of eggs mixed, coagulated, and

sterilized by the intermittent method. *Gelatin* cannot be used, as it melts at the temperature ( $37^{\circ}$  to  $38^{\circ}$  C.) required for growth. During incubation the tubes should be closed, so as to prevent evaporation.

*Immunity*.—Koch noted that by injecting killed cultures of the tubercle bacilli, after inoculation with living bacteria, the infected guinea-pigs improved in condition, and continued to live much longer than those animals not injected secondarily. He also discovered that a 50 per cent. glycerin extract of the cultures of the tubercle bacillus—tuberculin—produced the same effect as the dead cultures originally used. He announced the discovery of this substance in the hope that the prolongation of life observed to follow its use in the guinea-pig might also be true of man. Tuberculins obtained in various ways have been employed very extensively, with varying degrees of success. Some observers believe that the method is a very valuable one, while others claim that it is of little use. The tuberculin, when injected into persons suffering from chronic tuberculosis, is supposed to stimulate the formation of antibodies that will prevent further infection.

Tuberculin is much used in determining the presence or absence of tuberculosis. The more common methods are:

The *von Pirquet* reaction: In this a drop or two of Koch's old tuberculin is placed upon the skin, and a small scarification made through the drop with a sterile lancet. If the person is tuberculous, a small papule develops at the point of inoculation that is not unlike a vaccine papule. It is at first bright, then dark red, and remains for a week.

The *Morro* test consists in using the tuberculin in the form of a 50 per cent. ointment, made by mixing equal parts of "old tuberculin" and lanolin. This is rubbed into the skin without previous scarification.

*Calmette's* reaction, the "*ophthalmotuberculin*" test, consists of dropping 1 drop of a solution of prepared tuberculin into the eye of the suspected person. If no tuberculosis exists, no reaction occurs, but if the patient have tuberculosis, the eye becomes reddened within a few hours, and soon shows all the appearances of a more or less pronounced acute mucopurulent

inflammation of the conjunctiva. This attains its maximum in six or seven hours, and entirely recovers in three days. It usually causes the patient very little discomfort, but as a number of patients have suffered from supervening corneal ulceration and other destructive lesions of the eye, the test is now rarely used, the skin reactions being employed.

Attempts have been made to obtain an antituberculous serum by injecting animals with either dead bacilli or tuberculin. The results, however, have not been satisfactory, the serums seeming to have neither curative nor prophylactic value.

**Bacillus lepræ** is non-motile, non-flagellate, non-sporogenous, chromogenic, non-liquefying, non-aërogenic, aërobic, and acid resisting. It very closely resembles the tubercle bacillus in size and shape. It stains in very much the same way as the tubercle bacillus, but is not so resistant. Ordinary methods can be employed. It is more easily decolorized, however, by acids. With Gram's method it stains well.

*Pathogenesis.*—This is the organism that produces leprosy in man and monkeys; possibly in some of the lower forms of animals as well. The bacilli are found throughout the tissue lesions, and have been recovered from the blood of leprous individuals.

*Cultures.*—For many years attempts to grow this organism were unsuccessful, but recently bacteria believed to be the true bacilli of leprosy have been grown on artificial media. This is doubted by some investigators. The organisms obtained are acid fast, and in many respects resemble those found in the tissues. Others, however, may be classed among the diphtheroid, on account of their similarity to the *Bacillus diphtheriæ*.

According to Duval, the most successful method is as follows: Egg-albumen or human blood-serum is poured into sterile Petri dishes and dried for three hours at 70° C. The excised leprous nodule is then cut into thin slices, which are distributed over the surface of the coagulated albumen. By means of a pipet the medium is bathed in a 1 per cent. sterile solution of trypsin. The Petri dishes are now placed in a moist chamber and incubated for a week or ten days. The bits of tissue soften to a thick, creamy consistence and the bacilli multiply enor-

mously. They may then be transferred to serum-glycerin-agar or to ordinary agar plus 1 per cent. of tryptophan. The colonies on these media are moist and orange colored.

**Actinomycosis.**—The *Actinomyces bovis*, or *ray fungus*, is a non-motile, non-flagellated, liquefying, facultative, anaërobic, branched micro-organism belonging to the higher bacteria—the fungi.

The organism is large enough to be seen by the naked eye, appearing as small yellow particles. The fungus is made up of a central mass of granular substance in which are many structures resembling chains of cocci or spores. Extending from this center are many mycelial threads, terminating in club-shaped extremities.

It stains by the ordinary methods and by Gram's.

**Pathogenesis.**—This organism causes in cattle the disease known as “lumpy jaw” or “wooden tongue.” The disease may be communicated to man, the infection supposedly taking place by means of spores gaining entrance by inhalation, by food, or, what is probably more common, by way of decayed teeth.

**Cultures.**—It grows readily upon all the artificial media; best in the presence of air at a temperature of 37° C. On *gelatin* it grows feebly. Liquefaction takes place slowly and to a very slight extent. The colonies are small, grayish, and punctiform, with yellow centers and irregular outline. On *glycerin-agar* the growth appears after two days, and takes the form of small, yellowish-white, dry, wrinkled colonies, firmly adherent to the medium. These soon run together and form a broad, yellowish, wrinkled band, covered with rough projections. On *blood-serum* the colonies are small, whitish or yellowish, dry, firm, and often confluent. In *glycerin broth* white, granular, hemispheric colonies appear, and may grow as large as a pea. These fall to the bottom of the tube, leaving the medium quite clear. There is no surface growth. Does not coagulate *milk*. On *potato* small, colorless colonies appear in about a week.

*Actinomyces farcinica* and *Actinomyces maduræ* are two forms quite closely resembling the *A. bovis*, the first being pathogenic to the lower animals, the latter giving rise in man to

*madura-foot*, an affection characterized by induration, ulceration, and suppuration, with the formation of pus.

**Treponema pallidum** (*Spirochaeta pallida*) is an organism that is generally conceded to be the cause of syphilis. It has been found, by observers in all parts of the world, in the lesions of the primary and secondary stages; it is constantly present in the lesions of congenital syphilis; it is found in the blood of persons suffering from syphilis; and it is never found either in healthy individuals or in persons suffering from diseases other than syphilis. This organism is very delicate, actively motile, non-



FIG. 97.—SYPHILIS, CONGENITAL. HEART (Mallory).

*Treponemata pallida* in connective tissue and between muscle-fibers.

refracting, is long, thin, spiral or corkscrew shaped, with pointed ends. When stained they measure from 6 to 15  $\mu$  long by 0.25  $\mu$  across. Occasionally much longer forms are encountered, but these consist of several parasites attached to each other end to end. They show from six to fourteen turns, which are short, clear cut, and regular. Extremely delicate flagellæ have been demonstrated at the ends. No undulating membrane has been seen.

This organism stains with difficulty and, as a rule, very lightly; consequently, special methods have to be employed. In smears the best results are obtained with Giemsa's or Roman-

owsky's solutions. In tissues, Levaditi's method of nitrate of silver and pyrogallie acid gives beautiful results in formalin-fixed specimens, the treponemas staining black; the tissues, yellow. The most rapid and perhaps the most reliable method for finding the treponema is the examination with dark-ground illumination. Special apparatus is needed for this. The treponemas will stand out brightly against the black background of the preparation and are easily seen. Is Gram-negative.

*Pathogenesis.*—This organism is, without doubt, the cause of syphilis. As stated above, it has been found in the various lesions of the disease, and, now that it can be cultivated, Koch's postulates can be fulfilled. The disease has been reproduced experimentally in the higher forms of apes.

*Cultures.*—Until recently the treponema could not be cultivated artificially, but Noguchi has succeeded by using special methods. By inoculating syphilitic material into the testicles of rabbits he was able to get rid of contaminating organisms. Portions of this tissue are later transferred to a medium that consists of 1 part serum with 3 parts distilled water. The tubes are then incubated under anaërobic conditions. The treponemas begin to multiply after about forty-eight hours, and continue to increase slowly for four to five weeks. They attain their natural size in ten to twelve days, and later elongate and form tangled masses.

*Diagnosis.*—The method devised by Wassermann of applying the complement fixation-test has been used very successfully in diagnosing this condition. It has been determined that if a hemolytic system be added to a mixture of extract of syphilitic liver, heated syphilitic serum, and complement, no hemolysis occurs. The method is described fully under the heading of Wassermann Reaction (see p. 268).

*Spirochæta Refringens.*—This organism is very commonly associated with the *Treponema pallida* in the syphilitic lesions, but can be distinguished readily. It is larger and longer, and in the fresh condition is highly refractile. The turns of the spiral are fewer, longer, less regular, and flattened. The impression given is that of a piece of ribbon. Its movements are more rapid than those of the *Treponema pallida*, and it stains easily

with the ordinary dyes, and colors blue with Giemsa's solution instead of red or pink.

**Spirochæta balanitidis** has been found in cases of ulcerative balanitis, and would appear to be identical with the *S. refringens*.

**Spirochæta plicatilis** is a large, thick spirochete which stains easily. The curves are widely separated and large, and an undulatory membrane is present.

**Spirochæta Dentium.**—This spirochete multiplies in carious teeth, and more closely resembles the *Treponema pallidum* than any other species. In common with the *treponema* it is an organism of very delicate structure, only slightly refractile in the fresh condition, and the turns of the spiral are regular and permanent. It is, however, shorter than the *treponema*, its average length being 4 to 10  $\mu$ , and the turns of the spiral are closer together and not so deep. It also stains more easily than the organism of syphilis. According to Noguchi, there are at least two varieties: the *S. microdentium* and the *S. macrodentium*, the former being the one that resembles the syphilitic organism. In making smears for staining or for dark-field illumination, when the lesions are in the mouth, great care must be observed in order to prevent mistakes in diagnosis.

**Spirochæta buccalis** is a large organism with few undulations. Stains easily, and should give no difficulty in distinguishing between it and the *Treponema pallidum*.

**Spirochæta Vincenti.**—This spirochete, found in association with the fusiform spirilla (see p. 171), has the same characters as the *S. buccalis*. It must be regarded as either very closely related to, or identical with, that organism.

**Treponema pallidulum** (*Spirochæta pertenuis*) is an organism very closely related to that of syphilis. It is the cause of frambesia, or yaws, a contagious and inoculable disease very common in the tropics, and characterized by papillomatous lesions that do not involve the mucous membranes.

**Blood Spirochetes.**—Several forms of spirochetes have been noted as giving rise to the disease known as relapsing fever. At present the spirochetes found in this disease in different parts of the world are considered as belonging to different species, of which the following are distinguished:

*Spirochæta recurrentis* (*obermeieri*), the organism of European relapsing fever.

*Spirochæta duttoni*, the organism of West African relapsing fever (tick fever).

*Spirochæta novyi*, of the American type.

*Spirochæta carteri*, of East Indian fever, probably closely related to *S. recurrentis*.

If a drop of blood be taken during an attack of fever, numerous spirochetes will be seen between the red cells of the blood,

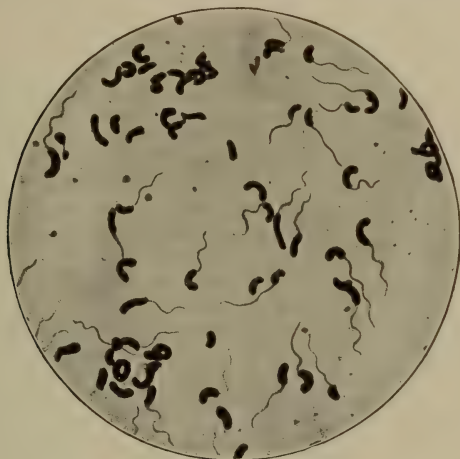


FIG. 98.—CHOLERA SPIRILLA, SHOWING FLAGELLA (Muir and Ritchie).

8 to 10  $\mu$  long, very slender, and pointed at the ends, each showing six to fifteen spirals. They are highly motile.

These organisms are taken into the body of biting insects and then transmitted to healthy individuals when bitten by the infected individual. Bedbugs, lice, and ticks may act as the carriers.

*Spirillum cholerae asiaticæ* is a motile, flagellated, non-sporogenous, non-chromogenic, liquefying, aërobic, and facultative anaërobic spirillum occurring in the form of short arcs, spirals, and "comma" forms. Is about 0.8  $\mu$  long, with one terminal flagellum.

Stains by the usual methods, but is Gram-negative.

*Pathogenesis.*—This organism is found in the feces only of those suffering from Asiatic cholera, and apparently gives rise to the symptoms of the disease on account of the liberation of an endotoxin. Filtrates from young cultures are said to be non-toxic, but in old cultures the bacteria are broken down by the formation of a bacteriolytic substance and the endotoxins set free. In guinea-pigs a peritonitis can be caused by the injection of the organisms into the abdominal cavity.

*Cultures.*—The cholera organism is easily destroyed by dilute chemical disinfectants; by light, heat, and drying; 60° C. for ten minutes kills. Large amounts of indol are formed in peptone solutions. It grows at all temperatures between 12° and 40° C., but best at 37° C. It grows on all the ordinary neutral or slightly alkaline media and ferments sugars. On *gelatin plates* the colonies are characteristic, and appear in the lower strata of the gelatin as small white dots. These slowly extend to the surface, causing liquefaction. In gelatin stabs small colonies appear along the line of inoculation. Liquefaction extends slowly from the surface downward, giving rise to an inverted cone with an air-bubble at the upper portion. The medium finally becomes completely liquefied. On *agar* there is a copious whitish growth which develops rapidly, but has no characteristic features. On *serum* the growth is rapid and the medium soon liquefies. In *milk*, acid is formed and the medium sometimes coagulated. On *potato* there is no growth unless the reaction is alkaline; then a thick, clear, brown streak is formed.

*Immunity.*—One attack of cholera usually leaves the individual immune. Haffkine has been able to bring about an immunity that seems to be followed by a positive diminution of mortality in protected cases. His method consists in the giving, subcutaneously, of a single inoculation of a virulent organism recently recovered from the peritoneum of a guinea-pig. The injection of bacterial extracts has also been employed. It was with the cholera vibrio that Pfeiffer was the first to demonstrate the bactericidal and agglutinating properties of the serum of immunized animals *in vivo*.

Spirilla resembling those of cholera are the following. They are found in water, and although in many cultural respects

resemble the spirillum of cholera, they are not pathogenic to man, and will not agglutinate with serum from an individual infected with cholera.

**Finkler-Prior Spirillum.**—Similar in shape, but shorter and stouter. Is actively motile. Grows rapidly, but does not produce indol; yet causes extensive liquefaction of gelatin. Is found in the feces of cholera morbus.

**Vibrio Tyrogenum.**—Similar in form. Growth and liquefaction faster than in *Spirillum cholerae*, but less rapid than the Finkler. Is actively motile. Forms yellow, irregular, distinctly circumscribed colonies. Is found in old cheese.

**Vibrio metchnikovii** is a spirillum closely resembling that of cholera. Growth very similar to that of cholera, but is slower. Is found in the feces in chicken-cholera. Is pathogenic for chickens, pigeons, and guinea-pigs.

**Bacillus fusiformis** is a long, rod-shaped organism measuring 5 to 10 by 0.6 to 0.8  $\mu$ , slightly swollen in the middle, and pointed at the ends. It stains readily with the ordinary dyes. The majority of observers state that it is Gram-negative, but others believe it to be Gram-positive. It is nearly always associated with the *Spirochæta vincenti* (see p. 248).

**Pathogenesis.**—This organism was described originally as occurring in cases of hospital gangrene. It is more common at present in the form of Vincent's angina (see p. 179), an inflammatory condition of the throat.

**Cultures.**—It has been obtained in pure culture by growing upon the surface of ascitic fluid agar under strictly anaërobic conditions at 37° C. After two or three days the fusiform bacilli appear in the form of delicately whitish colonies, resembling colonies of streptococci. It has also been grown on rabbit's blood agar, and on Löffler's blood-serum. From all of the cultures a somewhat offensive odor is given off.

Many observers believed for a long time that the *Bacillus fusiformis* and *Spirillum vincenti* were but different stages of the same organism. This has been finally proved by Tunnicliff, who found that in pure cultures of the fusiform bacillus, after forty-eight hours, there appeared spiral organisms resembling those seen in smear preparations from the original source

## CHAPTER XV

### INFECTION

By **infection** is meant the successful invasion of the tissues by an organism. The mere presence of the living agent within the body is not sufficient to cause infection; it must enter the tissues and give rise to symptoms that indicate a diseased condition. Trypanosomes may be even within the blood-vessels of certain animals and cause no symptoms.

There are normally many organisms contained within the body, particularly in the alimentary canal, but they give rise to no pathologic conditions until they leave their accustomed habitat.

Infection, therefore, means the entrance of organisms into the body, with subsequent injury to the tissues involved. By an infective disease is meant one that is the result of the entrance into and the multiplication of the organisms within the body.

The symptoms in such a condition are the result of the formation of toxins, and not of mechanical disturbances. As a rule, no symptoms appear immediately after the entrance of the invading organism into the body, as there is not sufficient toxin present. The interval between the inoculation and the symptoms resulting from the toxins is known as the *period of incubation*, which differs greatly in different diseases.

Then, too, infection may be influenced by certain peculiarities of the infecting organism and of the attacked individual. It is a well-recognized fact that true infection does not always occur after the primary invasion. This may be due to variations in the ability of the micro-organism to produce disease. Some have very little power to multiply after gaining entrance into the tissues, but they may form large amounts of poison. Other bacteria may form but little poison, yet have almost

unlimited powers of multiplication when in the body. The number of the organisms and the mode of entrance also effect the severity of the infection.

The infecting organisms may come from outside of the body—*exogenous*. They may enter the lungs in consequence of impure air or they may gain entrance into the body along with the food or water. Wounds of various sorts may carry the organisms into tissues; then, too, it has been discovered that diseases may be conveyed from one person to another by biting insects.

*Endogenous* infections are those resulting from organisms that are commonly present within the body. They may be due to some change in the tissues of the host, that allow these living bodies to escape from their normal surroundings and gain entrance into unusual localities. The colon bacillus that is normal in the intestinal canal may cause much trouble if it gets into other localities. It must be remembered that practically all openings communicating directly or indirectly with the external air will contain bacteria. They are normally present in the skin and the adjacent mucous membranes. The mouth and the intestines contain many varieties, while the stomach, on account of its acid contents, contains but few. The normal lungs are free from bacteria.

The results of bacterial invasion are much influenced by the local conditions at the point of attack—the avenue of infection. These are of the greatest importance in determining the occurrence or non-occurrence of infection. Certain bacteria, such as those of cholera, typhoid, and dysentery, attack only the intestinal canal, and will not cause trouble unless they first gain access to that tract. The gonococcus will not produce an infection in skin, even if that tissue be wounded. The tubercle bacillus in the lung can cause widespread destruction; in the skin little appears other than a localized tubercle.

Of the various obstacles to infection, an intact epithelial covering of the body inside and out is probably the most important. Such a covering is an efficient barrier against staphylococci and streptococci. An injury, nevertheless, need be but very slight in order to permit the organisms to enter. Such an injury may be secondary to the destructive action of prod-

ucts formed by the bacteria themselves. Associated infections may, likewise, be of importance. Tetanus organisms may not survive if inoculated alone into normal tissues, but will grow if pyogenic bacteria are also present. The same probably holds good with the diphtheria bacillus. Both of these, although unable to grow and multiply in an intact structure, can do so when these tissues have been previously or simultaneously bruised or lacerated. Although the epithelial coverings can protect, yet injuries to them are very common, and bacteria frequently gain entrance to the tissues. The question then arises, Why does not every infection become generalized and lead to the destruction of the host? There are two factors concerned in this problem. One is the *aggressive* or attacking force of the micro-organism, the other is the resistance which the host offers to the presence of the invader, to its multiplication, or to its ability to produce harmful substances. This resisting power is the *defensive* force.

*Aggressive Forces.*—Certain bacteria, as those of diphtheria and tetanus, are possessed of a very low grade of infectiousness, by which is meant their power of multiplying in the invaded body. The infection is almost always strictly local during the life of the individual; a general infection being exceedingly rare, and occurring as a terminal or a postmortem condition. The tetanus bacillus, particularly, is practically unable to maintain itself in normal living tissues. In cases of infection it owes its limited development either to the damage done by an associated infecting agent or by direct mechanical injury. Even then the organism has frequently disappeared from the body entirely at the time when the patient is actually dying from the effects of its brief sojourn. Evidently, its aggressive powers are minimal and, even though it kills through its highly poisonous toxin, the resistance which the animal body offers to its presence is entirely sufficient to prevent its active development. Similar conditions exist in regard to the diphtheria bacillus. It is questionable whether it can gain access to the deeper tissues through intact superficial structures, but by means of its own toxin it is evidently capable of causing marked destruction after that superficial barrier has been

passed. The above instances show that the infectious and toxic properties of an organism are two independent factors, which in the case of tetanus and diphtheria bear an inverse relation to each other.

An altogether different behavior is seen in a group of organisms represented by the anthrax bacillus and that of chicken-cholera. In these the local infection is followed almost immediately by a generalized infection, the organisms not only living, but actually multiplying freely in the body of the host. Their aggressivity, as compared with the previously mentioned type, is greatly developed, while their toxicity is practically nothing.

Between these two types already mentioned stand the cholera vibrio and the typhoid bacillus. Their aggressivity is quite well developed, particularly that of the typhoid bacillus, which is commonly present in the blood and tissues. In addition to their aggressiveness, the organisms of this class possess a well-marked toxicity, the effect of this appearing quite early in the course of the infection, and leading to a fairly characteristic clinical picture of the corresponding infectious disease.

Generally speaking, it may be said that the ability of micro-organisms to do harm depends upon the injurious nature of the substances they can produce. There are probably three groups of substances that are now recognized as of importance in connection with the clinical picture of the infectious diseases. They are:

1. True toxins or exotoxins, extracellular and soluble.
2. Endotoxins, intracellular and insoluble.
3. Bacterial proteins.

**Toxins.**—According to Ehrlich, the following are the characteristics of toxins:

1. They are extremely easily destroyed (labile) substances which occur as secretion products of vegetable or of animal organisms.

2. Their chemical nature is unknown. The impossibility of obtaining them in a pure form and their great lability render them insusceptible to ordinary chemical analysis.

3. An analysis of a toxin may be reached at present only through the medium of animal experiment.

4. The introduction of toxins into the tissues causes the formation of an antitoxin with the production of immunity. It has not been possible to obtain antitoxins for inorganic poisons, as the alkaloids.

5. In contradistinction to well-defined chemical poisons, the action of toxins is characterized by a latent or incubation period. The incubation period may be shortened experimentally by the injection of large quantities of toxin, but it cannot be eliminated entirely. Snake-venom, however, seems to act without an incubation period, but it is still to be classed with toxins because of its power to cause the formation of antitoxin.

6. The facts make it necessary to assume as a condition for the poisonous action of toxins a specific union with the protoplasm of the cells in certain organs. The affinity of other poisons, as alkaloids, for tissues depends not upon specific chemical union, but on some such process as solid solution or loose salt formation.

The true toxins cause the physiologic and pathologic disturbances as a result of their solubility and the ease with which they can diffuse throughout the animal juices. The two chief toxin producers are the organisms of tetanus and diphtheria. A few of the tetanus bacilli may cause no local disturbance, yet may bring about the death of the individual. Toxins produce specific symptoms; consequently, it may be assumed that they have special selective affinities for certain tissues, and produce their symptoms in consequence of such affinity. This can be shown experimentally: a mixture of guinea-pig brain and tetanus toxin will prove harmless, although there may be present several times the fatal dose of the toxin. Other toxins, instead of being specific for the motor nerve-cells, may act upon the red blood-cells, or upon the leukocytes, or upon the cells of the respiratory centers, for instance.

**Endotoxins** are insoluble substances not secreted by the living organism, but set free only after the death and disintegration of the parasites. They are not as specific in their action as the true toxins, but their injection into suitable animals gives rise

to the production of antitoxins which are capable of neutralizing the endotoxin employed. The toxic effect rapidly diminishes on keeping, and is seriously impaired by exposure to higher temperatures—55° to 60° C. Many symptoms of disease may be due to the breaking down of the organism with the liberation of these bodies.

**Bacterial proteins** constitute the main mass of the organism. They differ from the toxins and endotoxins in not conforming to the characteristics of either of the two. Their effect is essentially pyogenic, the formation of pus, and is one common to most, if not all, bacteria. In some animals the pyogenic action does not manifest itself, because death results too early, but in more resistant individuals it can be shown. These proteins in themselves are not markedly dangerous, but they have gained in importance since it has been demonstrated that the introduction of foreign albumins leads not to increased resistance (immunity) against such proteins, but to hypersensitiveness (anaphylaxis). Consequently, a subsequent injection after a certain interval of time may produce serious symptoms or death.

**Ptomaines** are nitrogenous compounds of basic nature and alkaloid-like properties, formed from animal matter in consequence of bacterial decomposition. Their formation is only possible when special food stuffs are directly available, while toxin production is, within certain limits, independent of the food supply, and represents a specific function on the part of the micro-organisms in question.

## THE CARDINAL CONDITIONS OF INFECTION

Infection can take place only when the micro-organisms are sufficiently virulent, when they enter in sufficient number, when they enter by appropriate avenues, and when the host is susceptible to their action.

**Virulence** refers to the disease-producing power of micro-organisms which depends upon the invasiveness of the bacteria, the toxicity of their products, or both. This property may vary greatly in different strains of the same variety of

organism. Most bacteria when grown in artificial media will not be as virulent as those grown in some animal. If, however, animal fluids are added to the culture-media the virulence may be retained or even increased. In order to increase the virulence, the best results can be obtained by the transplantation of the organism from one animal to another without any intermediate growth on culture-media. This method, however, increases the virulence of the organism only for that particular kind of animal used. Transference through rabbits increases the virulence for rabbits, but not for other kinds of animals. This increase can continue to a certain point, beyond which it will not go. The number of organisms which is necessary to kill the animal becomes progressively smaller, and the period of incubation, the time between infection and the first symptoms, shorter, until finally a strain is obtained in which the degree of virulence can no longer be increased by animal passage. This constitutes the "virus fixe."

**Number.**—The number of bacteria gaining entrance has a very important bearing upon infection, and may determine whether it shall occur or not. When bacteria gain entrance into an animal there will always be some of the organisms that are unable to withstand the defensive powers of the host, and consequently perish. Others may be so weakened as to be unable to cause trouble, while some will be able to overcome the resistance, and give rise to disease. The more virulent the organism, the fewer will be the number required to infect.

**Avenue of Infection.**—Local conditions are of the greatest importance in determining the occurrence or non-occurrence of infection. Cholera, typhoid, and dysentery attack the digestive tract alone. The gonococcus apparently can invade only through the mucous membranes of the genito-urinary apparatus or of the eye. The tubercle bacillus, although able to invade any tissue of the body, gives rise to modified forms of the disease. If it invades the skin a local condition known as *lupus* occurs. This may last for years without becoming general. The same organism entering the lungs can give rise to consumption, with extreme destruction of tissue and generalized

infections. Skin infections in general tend to remain localized unless the organisms have been implanted quite deeply, so as to more readily gain access to the circulation.

The chief obstacle to infection no doubt lies in the integrity of the epithelial coverings of the body, both inside and out. An injury, however, need be but very slight in order to allow the micro-organism to gain entrance.

**Susceptibility of the Host.**—This varies greatly, some animals readily succumbing to infection by a certain organism, while other animals will be distinctly resistant. This resistance, however, may depend very largely upon the physical condition of the invaded individual. If anything occurs that will lower the general physiologic activity, the individual will then be less able to withstand the attack of the organisms. *Fatigue* is an apparent factor. When tired out, from one cause or another, infection is much more likely to occur. *Exposure*, particularly to cold, is a very common cause of lowering the bodily resistance, and thus allowing infection. *Diet* appears to have some obscure effect in predisposing to certain diseased conditions. *Intoxication* by poisonous substances increases the susceptibility to infection. This is quite commonly seen in the frequency and fatality of pneumonia among excessive indulgers in alcohol. *Injuries* of all sorts render the possibility of infection to become greater.

When two different types of organisms invade the body at the same time the resulting condition is known as a *mixed infection*.

If after one organism has caused tissue changes, another gains entrance and gives rise to pathologic conditions, it is called a *secondary infection*.

## IMMUNITY

By **immunity** is meant the power to resist invasion by micro-organisms with the subsequent development of disease. An individual may be exposed to infection, but on account of some ability present may be able to resist and not acquire the disease.

The lack of resisting power is known as *susceptibility*.

One form of immunity is the *natural*, in which there is an inherited resisting power that is common to certain races of men or of lower living beings. The second type is the *acquired*, in which the immunity has been obtained after birth, and may be either active or passive.

Immunity is termed *active* when it results from the action of the cells within the invaded body, either in destroying the bacteria or in neutralizing their injurious products. It is that form which follows an attack of an infectious disease and which lasts for a varying period. It may be very brief, as in cholera; for a longer time, as in typhoid; or sometimes for life, as in small-pox. It may be due to accidental infection; to the inoculation of a weakened virus, as in vaccination; to the introduction into the body of bacterial products without the micro-organism; or it may result from the inoculation of dead bacteria, as in bacterination.

*Passive* immunity is always acquired, never natural. It is that which is obtained by the introduction of the serum of an immunized animal into the body of a non-immune individual. The serum should always be introduced parenterally, that is, into the blood, subcutaneous tissues, or endothelial cavities, never by mouth, as it would then be acted upon by the digestive juices. It is supposed that in the serum of the first there is a substance that neutralizes the bacterial products in the blood of the infected animal.

It must be remembered that immunity is a comparatively relative term. An animal may resist an ordinary dose, yet succumb if a very large amount, either of bacteria or toxin, be administered. The degree of immunity may be reduced by unhygienic surroundings, by fatigue, by exposure to abnormal temperatures, abnormalities of diet, drugs, pre-existing disease, and by injuries.

**Theories of Acquired Immunity.**—1. Pasteur and Klebs believed that the bacteria growing in the body used up some material that was necessary for their growth, and after dying left an unsuitable soil. This theory is not borne out by the facts.

2. Wernich and Chaveau held that in the growth of bacteria

there were elaborated substances that inhibited their future development or activity. This theory also does not hold.

3. The theory of phagocytosis. This is one of the most important, and is strongly supported by many well-known investigators. It, however, does not seem to be as satisfactory in general application as Ehrlich's "side-chain theory," which will be discussed later.

There are certain cells in the body that have the power of ameboid motion, by means of which they are able to surround

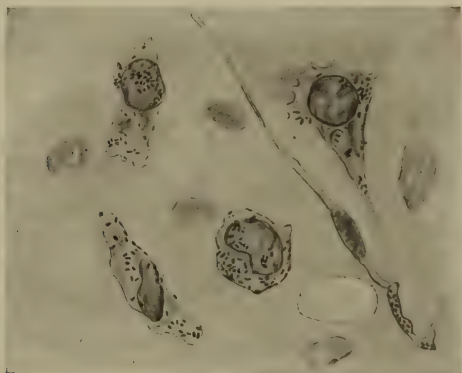


FIG. 99.—PHAGOCYTOSIS: THE OMENTUM IMMEDIATELY AFTER INJECTION OF TYPHOID BACILLI INTO A RABBIT.

Meshwork showing a macrophage, intermediate forms and a trailer, all containing intact bacilli (Buxton and Torrey).

and take up bacteria and destroy them. These cells are known as phagocytes. Metchnikoff believes that immunity is the result of the positive and negative chemotaxis (power of attraction) existing between phagocytic cells and micro-organisms. He divides such cells into two classes:

(1) *Microphages*—represented practically exclusively by the neutrophilic polymorphonuclear leukocytes.

(2) *Macrophages*—large mononuclear leukocytes, endothelial cells lining serous membranes, and fixed mononuclear cells of the spleen follicles and lymph sinuses.

The most active are the microphages, as they have the power of independent motion. When the bacteria gain entrance into the body the phagocytes are attached, and they attempt to

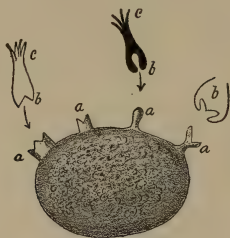


FIG. 100.

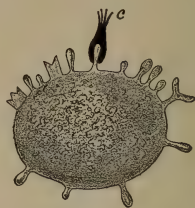


FIG. 101.

FIGS. 100 AND 101.—CELLS WITH VARIOUS RECEPTORS OR HAPTOPHOUS GROUPS OF THE FIRST ORDER.

(a) Adapted to combination with the haptophorous groups (b) of various chemical compounds brought to them. It will be noted that there is no mechanism by which the toxophorous elements of the molecules (c) can be brought to the cell.

ingest and destroy the invaders. If the immunity of the animal is marked, many of the organisms will be found within the cells; if the immunity is slight, few cells will contain bacteria. At one

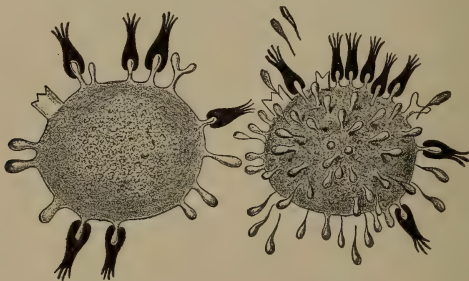


FIG. 102.

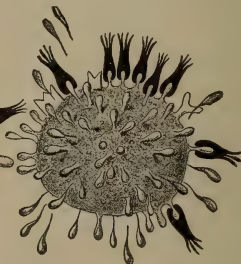


FIG. 103.

FIGS. 102 AND 103.—SHOW THE REGENERATION OF THE CELL-HAPTOPHORES OR RECEPTORS TO COMPENSATE FOR THE LOSS OF THOSE THROWN OUT OF SERVICE.

time it was claimed that phagocytes could take up only dead bacteria, but it has been demonstrated that the leukocytes can take up living organisms. As a rule, the bacteria are ultimately

destroyed, but on the other hand, the phagocyte may be the one to perish, and in this way permit a wide distribution of the invaders. Experiments have shown that the bacteria must be acted upon by a substance in the blood known as an *opsonin*, before the phagocyte is able to digest them.

4. Ehrlich's lateral chain theory. This receives its name from its analogy to the benzole ring in chemistry with the accompanying lateral chains. For convenience terms are used that can be applied to formed bodies, although they cannot be demonstrated as such in the body juices.



FIG. 104.—SHOWS THE NUMBER OF HAPTOPHORES REGENERATED BY THE CELL BECOMING EXCESSIVE, THEY ARE THROWN OFF INTO THE TISSUE JUICE.

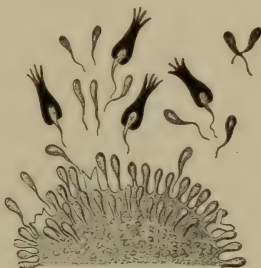


FIG. 105.—EXPLAINS WHAT ANTI-TOXINS ARE AND HOW THEY ARE FORMED.

The liberated receptors in the tissue juice and in the blood possess identical combining affinities with those upon the cell, and meeting the adapted haptophorous elements in the blood, combine with them, thus keeping them from the cells.

In this theory it is claimed that immunity depends upon the presence or absence of "receptors," the equivalent of the chemical lateral chains. The normal or fixed receptor is that body attached to the cell by means of which the cell is acted upon by various substances, nutritive or otherwise. Each receptor is supposed to be so formed as to unite with a certain body of a definite character. When the action of the bacteria upon the tissue cells is considered, it is supposed that the poisonous products consist of two portions, the "haptophorous" and

the "toxophorous" groups. The combination is thought to take place as follows: The haptophoric group unites with a certain definite receptor, and by so doing interferes with the normal function of the cell. At the same time the toxophoric group is able then to act directly upon the cell. If this group is very powerful the cell is destroyed, and if a sufficient number are involved the individual may die. When such a union occurs the receptors are of no further use. It has been found in such cases that in order to get back to the normal the cell

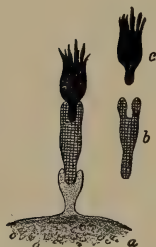


FIG. 106.—COMBINATION OF CELL (a), AMBOCEPTOR (b), AND COMPLEMENT (c).

The amboceptor may unite with the cell, but cannot affect it alone. The complement cannot unite with the cell except through the amboceptor, having no adaptation to the cell directly.



FIG. 107.

Cell with receptors of the second order (a) by which the cells fix useful molecules, of albumins, etc., on one hand (b), and zymogen molecules (c) on the other hand, and make use of the one substance through the action of the other.

will be so stimulated that new receptors similar to the ones destroyed will be formed. As a rule, a great excess of receptors will result, and many of these will be cast forth into the circulation, becoming free receptors. These cast-off receptors are what constitute an antitoxin, and, on coming in contact with the toxin molecule, unite with the haptophorous portion and consequently render it harmless. It being attached to a free receptor, it is no longer able to combine with a fixed receptor.

In bacteriolysis and hemolysis, or cytolysis in general, con-

ditions in which the destruction of actual cells is concerned, the destruction is brought about in a more complicated manner. Two other bodies than the cells are involved. One of these, known as the *complement*, is normally present in all serum. It is destroyed by a temperature of  $55^{\circ}\text{C}$ . for one-half hour, and is termed, therefore, thermolabile. The other, the *immune body*, or *amboceptor*, occurs in serum only as the result of the injection into the individual of the definite antigen. In other words, the amboceptor is specific in that it can combine only with that substance which gave rise to its formation. As it can resist heat up to  $80^{\circ}\text{C}$ ., it is termed thermostabile. In order that the cell be destroyed the complement unites with the specific amboceptor, which in turn joins with the fixed receptor, and the destructive action then occurs.

In active acquired immunity against foreign cells the invaded animal forms large amounts of amboceptor, which, being free within the blood, unite with and destroy the invading cells. If the supply is sufficient, the individual will recover. In passive acquired immunity large numbers of amboceptors in the serum from the immunized animal are directly introduced into the patient, and in this way effect a cure.

**Lysins** are those antibodies that will cause the destruction of cells, and they receive various names, according to the type of cell acted upon. The destruction is known as *lysis*. *Cytolysin* is the general name of all the substances that destroy the cells. A *bacteriolysin* causes lysis of bacteria; a *hemolysin*, that of erythrocytes.

It has been found, for example, that a "hemolysin" can be produced by injecting defibrinated rabbit's blood into a guinea-pig. The serum of the guinea-pig will develop marked ability to dissolve blood-corpuscles from the rabbit. This action can be destroyed by heating the serum to  $56^{\circ}\text{C}$ ., but the serum can be reactivated by the addition of fresh normal serum, as in it will be found complement. The immune serum will contain the amboceptor or immune body.

A. Foreign cells, blood, bacteria, etc.

B. Heated immune serum containing amboceptor, but no complement.

C. Unheated normal serum containing complement, but no amboceptor.

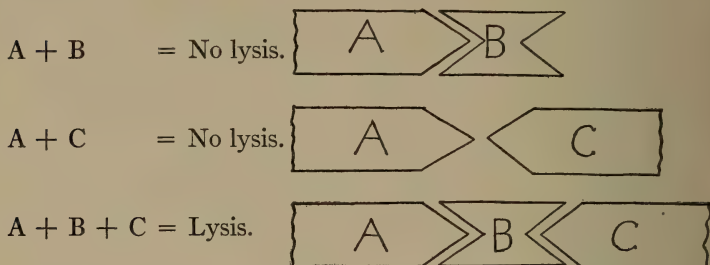


FIG. 108.—DIAGRAM REPRESENTING METHOD OF COMBINATION OF ANTIGEN (A), AMBOCEPTOR (B), AND COMPLEMENT (C) IN PRODUCING LYSIS.

In order to bring about the solution the three factors must be present. Experiments show that the complement cannot combine directly with the cell, but that there must be an intermediate substance, which is known as the amboceptor.

**Agglutinins.**—When bacteria or other cells are injected into the body there are formed within the serum definite substances, which when brought together with emulsions of the corresponding bacteria will cause the “clumping” or agglutination of the bacteria. If these are normally motile they will become less motile, and may lose that power entirely.

As the action is specific, it is commonly used for diagnostic purposes, especially in typhoid fever, when it is known as the “Widal reaction” (*q. v.*).

**Precipitins.**—It has been found that when an immune serum is brought together with a clear filtrate of a bouillon culture of the organism used for injection, there will appear a turbidity which will collect gradually at the bottom of the test-tube as a precipitate.

Such substances are formed whenever foreign albumins, either of vegetable or animal origin, are introduced through parenteral channels. These bodies are called precipitins.

These precipitins are specific in their reaction, and have been used for the purpose of identifying the origin of various

albumins. Under the term of the "biologic" blood-test this action has been employed in medicolegal cases to determine the source of blood-stains. It is also made use of in establishing zoölogic relationships between different animals.

If human blood is injected a number of times into a rabbit, the serum from the rabbit's blood will form a precipitate with normal human blood-serum when the two are mixed in a test-tube.

It is thought by some that the agglutinins and precipitins are practically similar substances; agglutination being a bringing together of cell; precipitin action, the bringing together of albuminous particles.

**Anaphylaxis** is a term applied to an increase of susceptibility to infection; it is the opposite of prophylaxis. It is a reaction that will occur with the parenteral form of injection of foreign proteins of any kind. In order to obtain the characteristic reaction it is necessary that a period of from six to ten days intervene between the first and second injection. A guinea-pig may be sensitized by 0.001 gm. of horse serum introduced into the peritoneal cavity. Eight to ten days later a second injection of 0.1 gm. of the serum is given, at which time the animal will become restless, short of breath, scratch itself violently about the nose, then depressed, and dies within one hour. Autopsy shows the lungs to be greatly distended and numerous small hemorrhages present. Similar symptoms have been encountered in people who have received antitoxin horse serum. In addition, there are skin eruptions, joint-pains, and edema, a condition known as serum sickness.

The anaphylactic reaction is specific, and the susceptibility, once acquired, may continue throughout the life of the animal, and may be transmitted by the blood of the mother to the offspring. It may be natural or acquired, active or passive. It may also be general or local.

The possibility of local anaphylactic reactions has been made use of in the diagnosis of various diseases, particularly tuberculosis. The subcutaneous injection of tuberculin in a non-tuberculous person will cause no disturbance. The same dose in the tuberculous will cause headache, muscle pains, fever,

and local reddening around the site of inoculation. Similar results are obtained if the tuberculin is instilled in the eye (Calmette reaction), but as severe inflammations have been occasioned, the method is not recommended. A like reaction is claimed when luetin, a specially ground-up culture of the *Treponema pallidum*, is employed as a subcutaneous reaction for syphilis. Much experimentation is being done along this line in respect to the making of diagnoses in various diseases. The symptoms of many diseases may be due to the presence of foreign proteins that have sensitized the individual.

According to Vaughan, anaphylaxis results when the strange protein in the blood reaches the cells and is slowly broken down by enzymic action. The cells, having once acquired the property of destruction, seize eagerly upon the protein the next time it is offered, disintegrate it rapidly, and so disseminate throughout the body the disintegration products, some of which may be toxic and account for the reaction.

**Complement Fixation.**—The well-known *Wassermann test* for syphilis is nothing more than the application of the complement-fixation reaction to diagnostic purposes. It is a method of making the diagnosis of syphilis by demonstrating in the blood (or cerebrospinal fluid, milk, or urine) of the patient a complement-fixing substance not present in normal blood.

The test is twofold: (1) A combination of syphilitic antigen, complement, and suspected serum. (2) A subsequent addition to the mixture of blood-corpuscles and hemolytic amboceptor. If the suspected serum contain the syphilitic antibody, the antigen and the complement unite with it, and the complement being thus "fixed," no hemolysis can take place upon the subsequent addition of the blood-corpuscles and hemolytic serum. If, on the other hand, the suspected serum contain no antibody, the complement cannot be fixed, and is, therefore, free to act upon the subsequently added blood-corpuscles in the presence of the hemolytic serum, and hemolysis results.

It is thus seen that the first test is made for the purpose of fixing the complement, and the second for the purpose of finding out whether or not it has been fixed.

The materials required for the Wassermann test are as follows:

A. Fresh sheep red blood-cells that have been thoroughly washed so as to get rid of any complement.

B. Blood-serum from a rabbit that has been immunized against the blood-cells of a sheep.

C. Immunized rabbit serum (B) that has been heated to  $56^{\circ}$  C. for thirty minutes in order to destroy the complement, but not affecting the specific amboceptor or immune body which can resist such a temperature.

D. Normal serum from a guinea-pig containing complement.

E. Antigen. Extract of the liver of a syphilitic fetus in alcohol, ether, or water; or lecithin, cholesterin, or extracts from organs of non-syphilitics.

F. Fluid suspected to contain syphilitic antibody (amboceptor). This should be heated to  $56^{\circ}$  C. for one-half hour to destroy the complement.

For the actual performing of the test there are also needed—

E 1. Serum from a known case of syphilis, containing, therefore, the syphilitic amboceptor. This also must be heated.

E 2. Serum from a known non-syphilitic.\*

Before using the solutions in the hemolytic series (C and D) they must be carefully standardized, so as to determine just what amount of amboceptor and of complement are necessary in order to cause hemolysis exactly. Such an amount is called a unit.

D, complement + E, syphilitic antigen + F, suspected fluid	}	Incubated for one hour at $37^{\circ}$ C. Then add	{	A, sheep corpuscles + C, hemolytic amboceptor.
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The combination of the two systems is placed in an incubator at  $37^{\circ}$  C. for one hour, then put in the ice-box for twenty-four hours, at the end of which time the final conclusions are drawn.

If F contains the syphilitic amboceptor, it will combine with both D, complement, and E, the syphilitic antigen. Consequently, when A and C of the hemolytic system are added, it will be found that the complement D has been already used or fixed. Therefore no free complement is present to unite

with A and C and cause hemolysis. *A positive Wassermann is indicated by the absence of hemolysis.*

If F does not contain syphilitic amboceptor the complement D will remain free, and when A and C are added, it will combine and cause the destruction (hemolysis) of the sheep corpuscles (A). *A negative Wassermann, therefore, is indicated by the presence of hemolysis.*

When there is no hemolysis the blood-cells will be in the bottom of the test-tube, and the liquid will be clear and colorless. In hemolysis there may be either a complete or a partial destruction of the red cells, and the overlying fluid will be of a reddish color, the degree depending upon the amount of cellular disintegration.

E 1 and E 2 are employed as controls in the series of tests necessary to determine the accuracy of the solutions that are used in the reactions above mentioned.

A positive Wassermann is nearly conclusive of there being a syphilitic infection. In active syphilis positive reactions have occurred in as much as 94 per cent. of the cases; in latent syphilis, 50 per cent.; and in chronic diseases of the nervous system, as general paresis and tabes dorsalis, the figures vary from 90 per cent. in the first to 50 per cent. in the latter.

On the other hand, a negative Wassermann does not exclude syphilis, as the result may be due to the treatment; as under active treatment with mercury and the iodids, salvarsan, or neosalvarsan the reaction is usually negative.

**Antitoxin Manufacture.**—As has been stated, if small doses of some special poison, such as diphtheria toxin, be repeatedly injected into a susceptible animal in increasing amount there will be developed in the blood-serum of that animal an antibody, called an antitoxin. This is formed by the cells and, according to Ehrlich's side-chain theory, corresponds to the free receptors. By injecting the antitoxin into an immunized animal it can resist a dose of toxin that ordinarily would be several times more than necessary to kill. That a combination occurs between the toxin and antitoxin can be proved by mixing the two together in a test-tube. The resulting mixture will prove harmless when injected into a susceptible animal.

Antitoxins are destroyed by heat, acids, and many chemicals, and gradually deteriorate spontaneously when in solution, particularly when kept at room-temperature. To preserve their activity the temperature should be not more than  $5^{\circ}\text{C}$ . Antitoxins are specific in that they neutralize the corresponding toxin and have no other apparent action within the body. The occasional ill effects, such as serum sickness, following the injection of antitoxic serums are due to other substances (the proteins in the serum) and not to the antitoxins themselves. Antitoxins may be injected subcutaneously, intravenously, into the subarachnoid space, into a nerve, into the brain substance, or into any of the body cavities. They are practically useless when given by the mouth, as very little is absorbed. As antitoxins, when injected into an organism, tend to disappear rather quickly, passive or antitoxic immunity is, therefore, transient; it cannot be depended upon for more than ten days or two weeks. When antitoxic serum is injected subcutaneously the antitoxin is absorbed slowly, requiring about forty-eight hours before it appears in the blood in maximum amount. When very prompt action is necessary the antitoxin should be introduced directly into the circulation by intravenous injection. Antitoxins are valuable both as curative and immunizing agents. For curative purposes they should be given early and in large enough doses to get their action before damage has been done by the toxins.

**Preparation of Diphtheria Antitoxin.**—As similar methods are used for practically all types of toxins, a description of the preparation of diphtheria antitoxin will be sufficient.

To obtain the necessary toxin virulent diphtheria bacilli are grown in alkaline bouillon containing 0.2 per cent. dextrose at a temperature of  $37^{\circ}\text{C}$ . for five to seven days. The bouillon culture is then passed through a porcelain or Berkefeld filter and stored in sterile containers in an ice-box. On account of general convenience horses are commonly employed. They should be perfectly healthy, free from glanders, tuberculosis, or tetanus. The horse is injected hypodermically with 0.1 c.c. of the toxic filtrate. This is frequently followed by a rise in temperature, local reaction, and some general disturbance. When these disappear, a second dose is given. The doses are cautiously

increased in amount and administered every few days until from 500 to 1000 c.c. of the toxin can be given without effect. When the degree of immunity is sufficiently high, blood is drawn from the jugular vein to the amount of from 3 to 9 liters, according to the size of the horse, collected in sterile bottles, then placed on ice for several days until the clear serum separates from the clot. This is then drawn off from the coagulated blood under aseptic precautions, and in it is the antitoxin. It is preserved by the addition of small amounts of phenol, trikresol, etc.; this latter seems to be the most satisfactory. After the serum has been obtained, its strength or potency, as expressed by the term "immunizing units," must be determined. An antitoxic unit may be defined as being *ten times the least quantity of antitoxic serum that will protect a standard (300-gm.) guinea-pig against ten times the least certainly fatal dose of toxic bouillon.*

To determine the strength of any given serum, the minimum fatal dose of a sterile toxin for a 300-gm. guinea-pig must be ascertained. Then must be determined the least quantity of antitoxic serum that will protect a guinea-pig against ten times the ascertained minimum fatal dose of the toxin. The necessary dose of antitoxic serum is expressed as a fraction of a cubic centimeter and multiplied by 10, the result equaling one unit.

Ehrlich, in determining the unit, makes use of a standard antitoxin (antitoxins not deteriorating or varying as do toxins) by which the antitoxin combining power of the test toxic bouillon is first determined. The toxin unit (*the smallest amount of toxin required to kill a guinea-pig weighing 300 gm.*) having been found, is then used to determine the antitoxic unit of antitoxins of unknown strength.

The power of antitoxic serums differ greatly: some contain 200 to 300 units per cubic centimeter, while others may contain even 1700 to 2000 per cubic centimeter.

Inasmuch as the antitoxin is only a small portion of the serum, various methods have been sought, by means of which the useless, and sometimes harmful, portions may be eliminated. The method employed at present in order to obtain such a concentrated antitoxin is that elaborated by Gibson—that of globulin precipitation.

**Tetanus Antitoxin.**—The method of obtaining is similar to that employed for securing the diphtheria antitoxin, the unit, however, being somewhat different. The use of this antitoxin has not been as satisfactory as that of diphtheria, on account of the rapidity with which the central nerve-cells combine with the tetanus toxin and the firmness of that union. Consequently, as a curative after toxic symptoms have developed, it is not very efficient, although more cases of tetanus do recover after antitoxin treatment than after any other form. Its chief value is as a preventive. It should be given as soon as possible after the injury has been received, in order that the free receptors will be present ready to combine with the toxin as soon as it has formed. By means of this prophylactic dose of antitoxin the number of fatal cases of tetanus infection following injuries received on the 4th of July has decreased very greatly.

**Bacterination** (bacterial vaccine) refers to the introduction within the body of measured amounts of sterile cultures of bacteria, in order that the individual may develop an immunity to that particular organism. This method has been employed in the infections of many varieties of bacteria, with particularly favorable results where the cocci have been the invaders. In pyorrhea alveolaris much success has been attained.

Two types of bacterins (vaccines) are employed, the *stock* vaccine and the *autogenous* vaccine. In the latter the bacterin is obtained by the cultivation of the organisms present in the lesion of the infected person. The stock vaccine is made of bacteria similar to those in the infected individual, but obtained from some other source. As a rule, better results are obtained by using the autogenous cultures, although in gonococcal infections the stock bacterin seems to be more satisfactory in many instances.

**Preparation of a Bacterin.**—The vaccine is usually prepared from a fresh twenty-four-hour growth of a pure culture of the micro-organism on an agar slant. The growth is scraped off and made into an emulsion with physiologic salt solution. The emulsion is then sterilized by heating at 60° C. for one hour and afterward is further diluted. This is done so that 1 c.c. will represent approximately the dose to be given. This dilu-

tion will vary, as the number of bacteria to a dose varies according to the organism used. Culture-tubes are inoculated with the vaccine and incubated for twenty-four hours at 37° C. to make sure that the sterilization was complete. To preserve the bacterin, 0.5 per cent. of carbolic acid or trikresol is used.

The injections should always be given subcutaneously. Usually three or four injections are given at intervals of from five to ten days, as in this way an immunity of much higher grade and longer duration is obtained. In most instances the acquired immunity lasts from two to five years and may be renewed.

Preventive inoculations with bacterial vaccines have been used extensively against typhoid fever, plague, and cholera.

The bacterins are used also as curative agents, but much care should be observed in giving the proper dosage. A minimum amount should be given, and if it creates no unfavorable reaction, a larger amount should be given subsequently.

**Opsonins.**—It has been shown that in the serum of persons convalescent from infectious diseases or vaccinated (by bacterins) against certain infectious diseases substances are present which prepare the micro-organisms for the action of the phagocytes. These substances are termed *opsonins*. If fresh blood is mixed with an emulsion of some bacteria, and then incubated for one-half hour, it will be found that many of the bacteria are within the polymorphonuclear leukocytes. If the serum is washed away from the leukocytes before adding the bacteria, none of the latter will be found within the leukocytes. In order to show that this effect is on the bacteria rather than on the leukocytes, the bacterial suspension may be treated with some serum for one-half hour, then washed free from this serum by means of salt solution and a centrifuge, and then mixed with some serum-free leukocytes; then it will be found that phagocytosis occurred as before.

The estimation of the opsonic power of the serum has been attempted and various methods elaborated. It may be questioned, however, whether any of the tests now in use is a true index of the amount of opsonins in the serum, although it may be taken to indicate roughly the measure of their activity.

## CHAPTER XVI

### LABORATORY TECHNIC

#### EXAMINATION OF FRESH MATERIAL

THE examination of fresh material may be made by teasing the tissue in water or, preferably, 0.6 per cent. saline solution. This, however, may not be satisfactory unless the tissue has been allowed to remain in some fluid long enough for the cells to become separated from the basement membrane. This is known as *maceration*; the following fluids are used for this purpose:

1. Alcohol, 33 per cent. (Ranvier), in which soak the specimen twenty-four hours.

2. Very weak chromic acid solutions, 1:10,000, or its salts. Müller's fluid is especially useful for nervous tissue. Leave in the acid twenty-four hours; in the latter, three to five days.

3. Osmic acid, 1 per cent., for twelve to twenty-four hours. Is useful if there is any fat present.

4. Potassium hydrate, 33 per cent., for from fifteen to twenty minutes. The specimen should be examined in the same fluid, as water distorts the cells. To preserve the tissue, wash in 50 per cent. acetic acid, then in water, and after staining in alum carmin can be mounted in glycerin. Is good for the examination of tissues or tumors that contain smooth, involuntary muscle-fibers.

5. Arnold's method: The small pieces of tissue are placed for five to ten minutes in 1 per cent. acetic acid, then for twenty-four to forty-eight hours in the weak chromic acid solution. They may finally be stained with picrocarmin.

Various reagents may be used in the examination of fresh specimens to render them transparent, to bring out certain details, or to cause various substances to disappear:

1. Glycerin clears the tissues and has the advantage of not changing chemically nor getting thin. Permanent mounts may be made by sealing the edges of the cover-glass with paraffin.

2. Potassium acetate in a saturated watery (50 per cent.) solution has a clearing action similar to, but less marked than, glycerin.

3. Acetic acid: Has the advantage that it causes the nucleus to shrink and the connective tissue to swell and become transparent. It does not affect fat, but dissolves the protein granules, so differentiates the two processes. Elastic fibers and micro-organisms are unaffected, so stand out prominently against the changed connective tissue. The acid may also be used to dissolve calcium salts. Solutions of 1 to 2 per cent. are generally employed, but the pure glacial acetic acid may be used.

A solution of acetic acid with fuchsin may be employed and in that way stain the nuclei.

4. Weak watery solutions of iodine. The following solution (Lugol's) is mixed with 3 to 5 parts of water:

Iodin.....	I
Potassium iodid.....	I
Distilled water.....	100

This brings the nucleus and the cell contour more plainly to view and also stains glycogen and amyloid particles brown.

5. Potassium and sodium hydrate solutions of from 1 to 3 per cent. have the power to dissolve most tissues, but do not affect elastic tissue, fat, bone, pigment, bacteria, or amyloid. Thirty-three per cent. solutions dissolve the cement substance and isolate the cells. This reaction takes place in a few minutes.

6. Osmic acid in 1 per cent. watery solution will stain fat black or brown.

7. Hydrochloric acid in from 3 to 5 per cent. is used for the recognition of lime salts, either in bone or in the tissues which it dissolves, with the production of bubbles of  $\text{CO}_2$ .

8. Fresh preparations may be stained by allowing a few drops of watery stains to pass under the cover-glass and then

washing out the excess. Methyl-green, Löffler's methylene-blue, or acetic acid fuchsin may be used. Hematoxylin is unsuitable.

## FIXATION AND HARDENING

If a more exact examination is desired, the tissues must be hardened and fixed. The material should be placed in the fluid used as soon as possible after it has been obtained. The point desired is that the conditions as they exist in the tissues during life shall be retained.

The different solutions vary greatly in their power of penetration and also in their effects upon different tissues. The action is facilitated by cutting the specimen in small pieces. After fixing and hardening it is generally necessary to thoroughly wash, so as to remove all traces of the agent employed.

The points to be observed are:

The specimens should not be more than 2 mm. in thickness.

The volume of reagent used should be from ten to fifteen times larger than the bulk of the specimen.

Place a layer of absorbent cotton or filter-paper in the bottom of the jar, so that the tissue may be acted upon by the fluid from all sides.

After sufficient hardening, remove the specimen and wash it in running water for twelve to twenty-four hours. It is then passed through alcohols of various strengths—70, 80, and 90 per cent., about twenty-four hours in each.

1. **Alcohol.**—It is used for rapid work and particularly if bacteria are suspected. It is not good for nervous tissue. Specimens should, as a rule, be put in weaker alcohol before being placed in absolute. This method is not used as much as formerly, on account of the shrinking and distortion of the tissues and the destruction of the red blood-corpuscles.

The so-called absolute alcohol is usually little more than 95 per cent. To extract the water, copper sulphate should be heated until the blue color disappears and then added to the alcohol. The alcohol should be filtered before using and the copper sulphate reheated when it begins to turn blue.

2. **Formalin.**—This reagent is being used very greatly in

place of alcohol. It has numerous advantages. The hardening takes place rapidly, the erythrocytes and other pigments retain their natural colors.

As formalin is bought it consists of a 40 per cent. solution of formaldehyd in water. The strength commonly used is a 1:10 or a 4 per cent. solution.

The tissues are left from four to six hours in the 4 per cent. solution, then thoroughly washed in water, and finally passed through alcoholic solutions of varying strengths.

Formalin is also used in combination with other mixtures, particularly as Orth's solution. This is made by adding 10 parts of formalin to 100 parts of Müller's fluid. This should be made fresh, as in the course of five or six days there is a crystalline precipitate formed. This fixes nuclear figures very well and hardens small pieces of tissue in from three to six hours. It is particularly important that they should be very carefully washed in running water. Is good for nervous tissues.

### 3. Müller's fluid is made up of:

Potassium bichromate.....	2.5
Sodium sulphate.....	1.0
Distilled water.....	100.0

This should be used in large quantities and should be changed every second day for about five times, and then be replaced whenever the solution becomes cloudy. To prevent the growth of mold 1 gm. of bichlorid of mercury should be added to 2 liters of the fluid.

For thorough hardening of small objects from ten to twelve weeks is required; for a large object, like the brain, a year. The process can be hastened by placing the preparation in an incubator and frequently changing the fluid.

After complete hardening the preparation is carefully washed in water, and then run through increasing strengths of alcohol. The sections stain well with hematoxylin and eosin. The red corpuscles are well preserved.

### 4. Erlicki's fluid consists of:

Potassium bichromate.....	2.5
Sulphate of copper.....	0.5
Distilled water.....	100.0

This fluid has the advantage that preparations will harden in from eight to ten days; and if in the incubator, in from four to five days. Its disadvantages over Müller's fluid are that it does not prevent shrinking as well and that there is frequently a precipitate in the tissues.

5. **Bichlorid of mercury** is of particular value in the fixation of cells and mitotic figures, but it has very little penetrating power. All the solutions that contain bichlorid have the drawback that there is a precipitation of mercury in the tissues that may be mistaken for pigment unless removed. These compounds may be dissolved by the addition of several drops of iodine to the 80 per cent. alcohol into which the specimens are put after having been washed. The iodine may be added to the alcohol in which the cut specimens are placed before being stained.

6. **Zenker's Fluid.**—

Bichlorid of mercury.....	5.0
Potassium bichromate.....	2.5
Sodium sulphate.....	1.0
Distilled water.....	100.0
Glacial acetic acid.....	5.0

The mercury and bichromate are dissolved in warm water and the sodium then added. It is best not to add the glacial acetic acid until the solution is ready to be used, as the acid rapidly evaporates.

After being in the fluid for twenty-four hours or less, according to the size of the specimen, it is thoroughly washed in running water twelve to twenty-four hours and then hardened in alcohol. The tissue should be passed through 80 per cent. alcohol containing iodine so as to remove the precipitate of mercury that forms.

Tissues prepared in this way stain according to all methods. The chromatin figures are well preserved as well as the erythrocytes.

7. **Osmic Acid.**—Its penetrating power is very slight, so very thin pieces of tissue, not more than 5 mm. in thickness, can be used.

A 1 per cent. watery solution is usually employed. It should be kept in the dark, and when the specimen is fixed, well washed. The paraffin method of embedding should be employed, using chloroform or clove oil, as the celloidin will dissolve out the fat. In clearing, do not use xylol, as it also dissolves fat.

#### 8. **Flemming's Solution.**—

Aqueous chromic acid solution (1 per cent.).....	15
Aqueous osmic acid solution (2 per cent.).....	4
Glacial acetic acid.....	1

The small bits of tissue are left in the fluid one to three days, well washed for several hours, then hardened in increasing strengths of alcohol. It is used for karyokinetic figures and for fat. Stains best with watery safranin.

9. **Hermann's fluid** is a modification of the above. A 1 per cent. platinum chlorid solution is used instead of the chromic acid. The nuclear figures are especially well preserved. The method of employment is the same as with Flemming's.

### DECALCIFICATION

**General Rules.**—The tissue must be well hardened before being put in the decalcifying fluid, otherwise it will be much altered. The formalin method is well adapted and small pieces should be used.

An excess of fluid should be used and it should be frequently changed. After complete decalcification the tissue should be carefully washed for two or more days. It must then be rehardened before it is ready to cut. The tissue is decalcified if it allows a needle to penetrate without meeting distinct resistance.

The following are the fluids commonly used:

1. **Chromic Acid and Its Salts.**—Müller's fluid for small pieces of bones or embryonal bones. It is a very slow process. Can be hurried by placing in an incubator.

2. **Saturated Watery Solution of Picric Acid.**—Requires about three weeks for embryonal bones. Larger and older

pieces take several months. Can be hastened by adding 3 to 5 per cent. of nitric acid. To remove the picric acid, wash the tissue, then place in 95 per cent. alcohol to which several drops of a saturated watery solution of lithium carbonate have been added. The fluid becomes colored and more carbonate should be added until it remains completely clear.

3. **Hydrochloric Acid.**—When used in 1 to 10 per cent. solution it works quite rapidly, but injures the tissues. Is best used as:

*Ebner's fluid:*

Hydrochloric acid.....	2.5
Alcohol.....	500.0
Distilled water.....	100.0
Sodium chlorid.....	2.5

This method can be hastened by increasing both the hydrochloric acid and sodium chlorid to 5 per cent.

4. **Nitric acid**, in from 3 to 10 per cent. in water or formalin, is well adapted for bone tissue from adults. The alteration to the tissue is less than when corresponding solutions of hydrochloric acid are used.

Haug recommends the following on account of its more rapid and better action:

Nitric acid, c. p.....	30.0-90.0
Absolute alcohol.....	700.0
Distilled water.....	300.0
Sodium chlorid.....	2.5

5. **Phloroglucin.**—This protects the tissues from the action of the acid, so that very strong solutions may be used. It acts very rapidly: small pieces are decalcified in one-half hour; larger ones, in several hours.

A stock solution is made consisting of:

Nitric acid, c. p.....	10 c.c.
Phloroglucin.....	1 gm.

This is carefully dissolved by warming; is best done under a hood. To this is added 100 c.c. of a 10 per cent. aqueous solution of nitric acid.

A more slowly working mixture is:

Phloroglucin.....	1
Nitric acid.....	5
Alcohol.....	70
Distilled water.....	30

*Thoma's method* is to:

1. Harden in Müller's fluid or alcohol.
2. Decalcify in:

Alcohol.....	5
Nitric acid.....	1

changing the solution very frequently.

3. Wash in alcohol.
4. Wash thoroughly in alcohol to which has been added an excess of calcium carbonate.

The decalcification requires from two to three weeks for large pieces. To remove the acid the tissue has to be in the carbonated alcohol from eight to fourteen days; should remain until there is no acid reaction with litmus-paper.

6. **Trichloroacetic acid**, used in 5 per cent. aqueous solution and frequently changed, decalcifies in from five to seven days; generally with good results.

## INJECTION

For the purpose of making them more easily studied the blood-vessels and other hollow structures may be filled with some injecting material that contains a stain. This procedure is not frequently used for pathologic purposes.

## EMBEDDING METHODS

The purpose of embedding is to give to a tissue a sufficient firmness to permit the cutting of thin sections. Two methods are commonly employed—one with celloidin, the other with paraffin.

Celloidin has the advantage of not requiring heat, and can be used for larger pieces of tissue. On the evaporation of the alcohol and ether a comparatively solid mass remains.

Paraffin can be used for small pieces of tissue only. It also renders the specimen brittle, so that it is frequently difficult to cut good sections. Although fluid when kept at the necessary heat, the paraffin becomes hard on cooling.

**Celloidin Method.**—In this process two solutions of celloidin of different thicknesses are employed—one of the consistency of syrup, the other of that of molasses. These solutions are made by adding to a mixture of equal parts of absolute alcohol and ether enough celloidin to give the desired consistency. The specimens must be thoroughly dehydrated in absolute alcohol and then placed in equal parts of absolute alcohol and ether for twenty-four to forty-eight hours. This latter step is not essential, but is advisable. From the alcohol the specimens are left in the thin celloidin at least twenty-four hours and in thick celloidin for a like period. If there is no hurry, the longer the time in each celloidin solution, the better will be the result. They are then placed on blocks, covered with thick celloidin, and allowed to harden. In the course of a few minutes, when the block can be turned upside down without the specimen sliding off, they should be placed in 80 per cent. alcohol. After remaining there for several hours they are ready to cut.

The blocks best adapted for use are those made out of vulcanite or hard paraffin. The latter are particularly convenient. A square of hard paraffin is cut up into blocks of various sizes and the tops roughened with a knife so as to give a better surface for the celloidin to adhere to. Cork and wood are not well adapted, as after being in the alcohol for any length of time the tannic acid is extracted; it penetrates the specimen and interferes with its staining properties.

In cutting celloidin sections the knife is clamped at a very marked slant, so that as much of it as is possible will be used. The blade and the specimen should be kept constantly wet with 80 per cent. alcohol. As the sections are cut they are lifted off the knife with a camel's-hair brush and placed in a dish containing water. This causes them to flatten out.

After the staining has been completed the sections are passed through graded alcohols to remove the water and are then placed in some fluid that will clear them. Clove oil should

not be used, as it dissolves the celloidin. Bergamot, cedar oil, creosote, and xylol, alone or in combination with 1 part of carbolic to 3 parts of xylol, do not affect the celloidin.

Summary:

1. Dehydration in absolute alcohol.
2. Absolute alcohol and ether, equal parts, one to three days.
3. Thin celloidin, one to five days.
4. Thick celloidin, one to five days.
5. Mount on block.
6. Alcohol (80 per cent.), twelve to twenty-four hours.
7. Cut on microtome.
8. Stain, dehydrate, and clear.
9. Mount in balsam.

**Paraffin Method.**—The preparation must be thoroughly dehydrated in absolute alcohol or anilin oil. It is then placed in some fluid that is a solvent of paraffin—xylol or chloroform are commonly used—for four to five hours. The fluid should be changed several times. Then it is put in a mixture of chloroform or xylol and paraffin for two to three hours. The infiltration is hastened by heating the mixture at about 50° C. It is then placed in paraffin that melts at about 50° C. for three to five hours, the paraffin having been changed once or twice. The melting-point can be varied by making combinations of paraffin that melt at different degrees. The two generally used are one of 56° C. and another of 45° C. In warmer weather a paraffin with a higher melting-point is used.

The specimen is taken and placed in a little paper box in which a small amount of paraffin has been poured. When the tissue has been properly arranged, more paraffin is added. The box is then placed in a dish of cold water, so that it will be rapidly cooled. This prevents crystallization and brittleness. Instead of using the paper boxes two right angles of metal are put on a glass plate so as to form an enclosure. Paraffin is poured in to form a thin film, then the tissue, and finally more paraffin.

After cooling, the specimen is fastened on a block of vulcanite or hard paraffin by heating its surface, and is then cut on the microtome. The blade is held at a right angle if the specimen

is small, on a slant if large, and the cutting is done dry, no alcohol being used.

Summary of the paraffin embedding:

1. Dehydration in absolute alcohol.
2. Xylol or chloroform four to five hours, changing the fluid a couple of times.
3. Xylol or chloroform and paraffin, two or three hours.
4. Melted paraffin in hot chamber at  $50^{\circ}$  C. for three to five hours. Change once.
5. Block and quickly cool.
6. Cut.

The paraffin sections are so brittle that they cannot be treated in the same way as the celloidin ones. The best method is to take the section and place it in a dish containing water at about  $45^{\circ}$  C. This causes the specimen to flatten. A perfectly clean slide is then smeared with a very fine film of glycerin-albumin and is slipped under the floating section. The excess of water is drained off or carefully touched with blotting-paper and the slide is then placed in the incubator at  $37^{\circ}$  C. for three to five hours.

The paraffin should be removed before staining the section. This is hastened by holding the slide over a small flame until the paraffin becomes transparent, when it is placed in xylol or turpentine for about two minutes. From there into absolute alcohol for about five minutes. It is advisable but not necessary to put the slides into weaker alcohol before beginning the stain. When the above steps have been gone through the tissues may be stained any way that is desired.

*Glycerin-albumin* solution for fastening paraffin sections to the slide is made as follows: The white of an egg is well beaten and to it is added an equal volume of glycerin. These are thoroughly mixed and filtered. It is used by smearing a very thin layer on the slide, the paraffin section is placed on it and then heated up to a temperature of about  $60^{\circ}$  C. until the albumin coagulates. If the sections have been taken from water it must be allowed to evaporate before the coagulating is done. The evaporation will be hastened by placing the slides in the incubator.

## CUTTING SECTIONS

**Freezing Microtome.**—This method is valuable for rapid diagnostic work, but sections cannot often be cut sufficiently thin to allow a careful examination of the details.

The piece of tissue used should not be more than 4 mm. high and it must be free from all traces of alcohol. The alcohol is removed by placing the specimen in a large amount of water that is of a temperature of about 30° C.

The specimen is placed on the metal stand and a spray of ether or of carbonic acid gas is directed against the under side. The tissue is held in place by lightly pressing upon it with some flat piece of wood, as the handle of a small scalpel. Care must be taken not to freeze the tissue too hard or it will be so brittle as to break or show irregular streaks. The cut sections should be placed in 80 per cent. alcohol, as they will unroll better than if put directly into water.

The freezing method is particularly well adapted for tissues that have been hardened in Müller's fluid, as there is no change in the finer characteristics. Formalin is very useful, as it permits very good sections to be made and is employed especially in the rapid diagnosis of tumors.

A rapid method is as follows:

1. Take a small portion of the tissue that has been removed at the operation and place immediately in a 10 per cent. solution of formalin for about two minutes.
2. Freeze; put the sections into water to flatten.
3. Stain in lithium carmin two to three minutes.
4. Blot stain and mount in glycerin.

**Serial Sections.**—*Paraffin.*—The block containing the specimen is turned until the anterior and posterior edges are parallel; as much of the paraffin being removed as is possible. The knife is placed at right angles and with rapid strokes the sections are cut. The edges of the sections cling to each other and long ribbons may be cut. These ribbons should be carefully placed on sheets of toilet paper, carefully numbered and marked, so that the beginning of each series can be determined. The ribbons are divided into lengths convenient for placing on the

slide. They are then floated on water and picked up on the slide covered with the glycerin-albumin.

## STAINING

The principle of staining depends upon the different affinity of certain portions of the tissue for special dyes, so that they become more evident for purposes of study. There are certain stains which show a distinct affinity for the nuclei, while others select the cell protoplasm and the intercellular substance. By employing two stains a double coloring is obtained. In some conditions a single color may affect different portions of the tissue differently.

According to their reaction, stains are divided into the basic, which are commonly nuclear or chromatin stains, and the acid, those that affect the cell protoplasm or the intercellular tissue. Neutral stains are generally artificial combinations of some of the above two.

After being stained it is generally well to differentiate. Although a stain may be a nuclear one, yet there is usually some effect upon the other substances, the same holding true in regard to the acid stains. To remove this color, certain fluids are used, as water, weak solutions of acid in water or alcohol, alcohol, anilin oil, and tannic acid.

It is also necessary that the sections shall be rendered transparent, and this is brought about by placing them in xylol, carbol-xylol, oil of cloves, creosote, or bergamot.

Certain general rules should be observed:

1. All staining fluids should be filtered before use to avoid precipitates in the tissue. Good stains should be used; the best being those of Dr. Grübler, of Leipzig.

2. The sections should be spread out in the stain and should not lie upon each other, as the fluid is then likely to stain unevenly. Large amounts of stain in large dishes should be employed. It is also an advantage to carefully move the sections to and fro.

3. The time required for staining varies, as a rule being less in old, well-ripened stains than in others freshly prepared. This

depends also upon the proper hardening and fixation of the tissue and also upon its age. Fresh tissues will stain more deeply and more quickly than old ones.

4. The staining of refractory tissues may be assisted by:

(a) Concentration of the stain.

(b) Staining for a longer time, up to twenty-four hours.

(c) Heating up to  $37^{\circ}$  C.

(d) Adding mordants, as acids and alkalis, anilin oil, etc.

5. The sections should be carefully washed in water to remove all traces of the decolorizing agents used.

6. Sections should be thoroughly dehydrated before being mounted; otherwise those areas containing water will not be transparent and will contain what appear to be oval pigment particles.

Method of staining and mounting sections:

1. Stain.

2. Wash, usually in distilled water.

3. Alcohol (80 per cent.) two to three minutes.

4. Alcohol (95 per cent.) three to five minutes.

5. Absolute alcohol two to three minutes.

6. Clearing fluid until the specimen sinks below the surface, two to three minutes.

7. Place section on slide, blot off the excess of clearing fluid, and mount in balsam, using a cover-glass.

## NUCLEAR STAINS

### Aqueous Alum Hematoxylin Solution.—

Hematoxylin crystals.....	1 gm.
Sat. aq. sol. ammonia alum.....	100 c.c.
Water.....	300 "
Thymol.....	a crystal

Dissolve the hematoxylin in a little water by the aid of heat. After the solutions have been mixed, expose to the light and air in an unstoppered bottle for about ten days. Then tightly cork.

**Delafield's Hematoxylin.**—

Hematoxylin crystals.....	4 gm.
Alcohol (95 per cent.).....	25 c.c.
Sat. aq. sol. ammonia alum.....	400 “

Dissolve the hematoxylin in the alcohol, then add the alum solution. Expose the mixture to the air and light four to five days. Then filter and add:

Glycerin.....	100 c.c.
Alcohol (95 per cent.).....	100 “

Expose to light and air for a couple of weeks, then filter and keep tightly corked. The solution lasts well and stains the more rapidly the older it gets.

**Ehrlich's Acid Hematoxylin.**—

Hematoxylin crystals.....	2 gm.	} saturated with am- monia alum.
Absolute alcohol.....	60 c.c.	
Glycerin.....	60 “	
Water.....	60 “	
Glacial acetic acid.....	3 “	

The solution is ripened in an uncorked bottle until it becomes deep red in color; requires a couple of weeks. If kept in well-stoppered bottle precipitates do not form and the solution retains its staining powers for years. Also does not overstain.

**Mayer's Hematein.**—When hematein is used, ripening is unnecessary, but the results from such stains are not as satisfactory as when hematoxylin is used:

Hematein.....	0.4 gm.
(Dissolve in a few drops of glycerin.)	
Alum.....	5.0 “
Glycerin.....	30.0 c c
Water.....	70.0 “

**Hematoxylin Staining.**—The nuclei are stained blue. The older the solutions, the quicker they act and the deeper they stain. If the sections are overstained, the excess of color can be removed by placing them in hydrochloric acid alcohol until the proper color is obtained. The acid causes the blue to change to a brown, but the color is regained when the sections are placed in water. The acid should be thoroughly washed out;

this can be hastened by using water to which an equal amount of a saturated watery solution of lithium carbonate has been added.

1. Stain three to ten minutes, according to age of stain.
2. Wash thoroughly.
3. Differentiate with acid alcohol, about thirty seconds if sections are overstained.
4. Wash thoroughly.
5. A counterstain, eosin, is usually employed.
6. Dehydrate, clear, and mount in balsam.

#### **Alum Carmin.—**

Carmin.....	1 gm.
Alum solution (5 per cent.).....	100 c.c.

Boil for one-half to one hour and when cool filter. It stains the nuclei a violet red. There is no danger of overstaining and the color is not very easily removed in water or weak acid solutions. This preparation does not work well with objects that are difficult to stain.

The sections are placed:

1. In the stain for ten minutes to two hours.
2. Then washed thoroughly in distilled water.
3. Dehydrated in alcohol, cleared, and mounted.

#### **Lithium Carmin.—**

Carmin.....	2.5 to 5.0 gm.
Sat. sol. lithium carbonate.....	100.0 c.c.

Heat and filter. The nuclei are stained an intense red. Is well adapted for tissues that stain with difficulty. Any excess of color can be removed in acid alcohol. Is a good counterstain for tissues that have been injected with blue substances.

Sections are placed:

1. In the stain for two to three minutes.
2. Washed in water.
3. Differentiated for one-half to one minute in acid alcohol; hydrochloric acid, 1; 70 per cent. alcohol, 100.
4. Washed thoroughly so as to remove the acid.
5. Dehydrated in alcohol, cleared, and mounted in balsam.

**Picrolithium Carmin.—**

Lithium carmin solution.....	1 part
Sat. watery sol. picric acid.....	2 parts

Sections are:

1. Stained three to five minutes.
2. Washed.
3. Differentiated two to three minutes acid alcohol.
4. Washed thoroughly.
5. Dehydrated in alcohol that has had a little picric acid added to it.
7. Cleared and mounted.

Nuclei are stained brownish red, and the protoplasm yellow.

**Borax Carmin.—**

Carmin.....	0.5 gm.
Borax.....	2.0 "
Distilled water.....	100.0 c.c.

Mix and heat until boiling begins; should be stirred constantly; then add 4.5 parts of dilute acetic acid (0.5 per cent.) and let stand twenty-four hours; then filter.

This gives the same results as the lithium carmin except that the color is not so intense.

Sections placed:

1. In stain for five to fifteen minutes.
2. Washed in water.
3. Differentiated one-half to one minute in acid alcohol solution.
4. Washed in water thoroughly to remove acid.
5. Dehydrated, cleared, and mounted.

**Bismarck Brown.—**

Either a 3 to 4 per cent. watery solution obtained by boiling and filtering.

Or a concentrated alcoholic solution made in 40 per cent. alcohol, equal to  $1\frac{1}{2}$  to 2 per cent.

Sections are:

1. Stained five minutes.
2. Washed in alcohol or 1 per cent. hydrochloric acid alcohol.
3. Dehydrated, cleared, and mounted.

The nuclei are stained a deep brown; the protoplasm, a lighter color. Bacteria are an intense brown. Cannot over-stain. This method is especially adapted for micro-photographic work.

**Gentian-violet.**—Either a 1 per cent. watery or a 2 per cent. alcoholic solution may be used. Are likely to overstain.

Sections are:

1. Stained three to five minutes.
2. Washed in alcohol until they become a pale blue.
3. Then in absolute alcohol.
4. Cleared and mounted.

The nuclear staining is clearer if the sections are put for fifteen to thirty seconds in a 0.5 per cent. solution of acetic acid and then into the alcohol.

**Safranin** is usually employed after fixing in Flemming's solution to bring out karyokinetic figures.

Sections:

1. Stained one-half to twenty-four hours in a 1 per cent. watery solution of safranin.
2. Quickly washed in water.
3. Washed in absolute alcohol to which 5 to 10 drops of 1 per cent. hydrochloric acid alcohol have been added.
4. Washed in pure absolute alcohol until the section is a clear brown.
5. Cleared and mounted in alcohol.

The resting nuclei are pink, those undergoing mitotic changes are deep red.

Another method is:

Anilin oil.....	2 C.C.
Water.....	100 "
Safranin in excess.	

Heat to 60° C. and filter. The solution will last about two months. This form stains almost immediately. The after-steps are as above.

### DIFFUSE AND DOUBLE STAINING

Double staining is employed for the purpose of obtaining a contrast between the nuclei and the plasms and interstitial substance. The nuclear stain is employed first, as the contrast stain is weaker and colors the tissues more diffusely.

#### Neutral Carmin.—

Carmin powder.....	5 gm.
Aq. ammon. fort.....	1 c.c.

These rubbed together, then add:

Distilled water.....	200 c.c.
----------------------	----------

Boil until the ammonia is driven off. Allow the solution to stand uncorked for about a week, then filter. The solution works better as it becomes older.

To prepare the stain for immediate use add just enough ammonia to the carmin to make a paste. This should be thinly spread on the sides of the mortar and allowed to dry. Pulverize again, let it remain exposed to the air for twenty-four hours, then dissolve in cold water; it is then ready for use.

To stain sections: Add the stock solution to distilled water until a clear pale red color results. The sections remain in this until they become plainly red, up to twelve hours. The best results are obtained by staining for a long time in a weak solution. Strong solutions stain more rapidly. Wash thoroughly in water, dehydrate, clear, and mount.

The counterstain best used is hematoxylin, and it should be employed first.

**Eosin.**—Either the form soluble in water, which is the better, or that in alcohol may be used. A few drops of a concentrated solution of either variety is added to a small dish of water and the sections stained until they are of a reddish color—one to three minutes.

Then washed in water.

Dehydrated in alcohol. Should be careful not to leave in the alcohol too long, as it gradually dissolves out the stain.

Cleared and mounted.

This method is preceded by staining in hematoxylin. In such cases the nuclei are blue. In specimens fixed in formalin

or sublimate solutions the red blood-cells stain a bright red or copper color and the blood-vessels are prominent. Eosinophile cells show up plainly. The other tissues show a diffuse reddish tinge.

**Picric acid** is generally used in combination with some other stain, as in Van Gieson's method. As the picric acid decolorizes the sections, they should be overstained in the hematoxylin. If iron hematoxylin is used instead of Delafield's, the decolorization does not occur to the same extent.

Van Gieson's method for nervous tissue:

Aqueous sol. acid fuchsin (1 per cent.)	15 c.c.
Sat. aq. sol. picric acid	50 "
Water	50 "

For connective tissue:

Aq. sol. acid fuchsin (1 per cent.)	5 c.c.
Sat. aq. sol. picric acid	100 "

Sections are:

1. Overstained in Delafield's hematoxylin.
2. Washed thoroughly in water.
3. Stained in Van Gieson solution three to five minutes.
4. Washed in water one-half minute.
5. Dehydrated, cleared, and mounted.

Nuclei are stained brownish red; connective tissue, varying shades of light red; axis-cylinders, brownish red; myelin sheaths, yellow; neuroglia and sclerosed fibers, red; amyloid, rose or reddish brown; hyaline, red; colloid, orange or red.

### CONNECTIVE TISSUE STAINS

**Van Gieson's stain**, as already given, may be used. The best results are obtained after fixation in chrome salts or sublimate solutions; are not so good after alcohol.

**Mallory's anilin blue stain** gives good results after fixation in Zenker's fluid or sublimate solutions. The fibrillæ and reticulum of connective tissue, amyloid, mucous, and other hyaline substances stain blue; the connective tissue can be differentiated from the other substances by their form. Nuclei, protoplasm, fibroglia, fibrils, axis-cylinders, neuroglia fibers, and fibrin stain

red; erythrocytes and myelin sheaths, yellow; elastic fibers, pale pink or yellow.

Sections are:

1. Stained in a 0.1 per cent. aqueous solution of acid fuchsin five or more minutes.
2. Transfer to the following solution and stain twenty minutes or more:

Anilin blue soluble in water (Grübler).....	0.5 gm.
Orange G. (Grübler).....	2.0 "
Aqueous solution of phosphomolybdic acid (1 per cent.) .....	100.0 c.c.

3. Wash and dehydrate in several changes of 95 per cent. alcohol.
4. Clear in xylol or in oil of origanum (Cretici).
5. Balsam.

#### ELASTIC FIBER STAIN

**Weigert's Stain for Elastic Fibers.**—It is best to buy the stain already made up, as its preparation is rather difficult.

The sections are:

1. Stained in the above solution for twenty minutes to one hour.
2. Washed off in alcohol.
3. Blotted with filter-paper, xylol added, and blotted two or three times until the section is clear.
4. Mounted in balsam.

The elastic fibers are dark blue, almost black.

**Unna's Orcein Stain.**—

Orcein.....	1 gm.
Hydrochloric acid.....	1 c.c.
Absolute alcohol.....	100 "

Sections are:

1. Stained six to twenty-four hours.
2. Washed thoroughly in 70 per cent. alcohol.
3. Washed in water to get rid of the acid.
4. Dehydrated, cleared, and mounted.

The elastic fibers are a deep silky brown color; connective tissue, a pale brown. This method has the advantage that

elastic fibers that have degenerated into elacin take the basic blue stain.

**Levaditi Stain for *Treponema Pallidum*.—**

1. Fix small pieces of tissue, 1 to 2 mm. thick, in 10 per cent. formol for twenty-four hours.
2. Wash in water a few minutes; place in 95 per cent. alcohol for twenty-four hours.
3. Wash in distilled water until the tissue sinks.
4. Place in a 2 per cent. solution of silver nitrate and put in an incubator at 38° C. for three to five days. It is best to use amber-colored bottles.
5. Wash briefly in distilled water, then put in the following solution for twenty-four to forty-eight hours at room-temperature:

Pyrogalllic acid.....	3 gm.
Formalin.....	5 c.c.
Aq. dest.....	100 "

6. Wash in water, dehydrate, and embed in paraffin. The treponema will stain black; the rest of the tissue, yellow.

**Kaiserling's Method of Preserving Natural Colors in Tissues.**

1. Fixation for one to five days in—

Formaldehyd.....	200 c.c.
Water.....	1000 "
Nitrate of potassium.....	15 gm.
Acetate of potassium.....	30 "

Change the position of the specimen frequently. The time of fixation varies with the tissue or organ and the size of the specimen.

2. Drain and place in 80 per cent. alcohol one to six hours, and then in 95 per cent. alcohol for one to two hours, to restore the color.
3. Preserve in—

Acetate of potassium.....	200 gm.
Glycerin.....	400 c.c.
Water.....	2000 "

Exposure to light gradually affects the colors.

## BLOOD STAINING

Before being stained the blood must be fixed to the slide either by heat or by some chemical.

**Heat** may be used in all cases except when Wright's stain is employed; it must be used with Ehrlich's triple stain to get good results. The films should be exposed to a dry heat of from 100° to 110° C. for ten to fifteen minutes.

**Chemicals.**—The smears are fixed in absolute alcohol or ether or a mixture of equal parts of the two for five to ten minutes. Then dried and stained.

**Stains.**—*Wright's*.—It is best to procure this stain ready made. It is employed as follows, as no previous fixing is necessary:

The unfixed film is covered with the solution and stained for a minute. Distilled water is added drop by drop until a metallic scum appears on the surface of the fluid and is allowed to remain two to three minutes. Then wash the film, which is a deep blue or purplish color, until it becomes yellowish or pink. Dry between blotting-paper and mount in balsam.

The erythrocytes will be stained orange or pink; the nuclei of the leukocytes, blue; neutrophile granules, lilac; eosinophile granules, pink; fine basophile granules, deep blue; coarse mast-cell granules, deep purple. The malarial organism stains blue.

*Ehrlich's Triacid.*—Best bought ready made.

After fixing with heat, stain five to eight minutes; wash in running water, dry, and mount.

Erythrocytes stain orange; nuclei of the leukocytes, greenish blue; neutrophile granules, violet or lavender; eosinophile granules, copper red; basophile granules are unstained.

*Polychrome methylene-blue* (Goldhorn's) is bought ready made.

After fixation for fifteen to twenty seconds in methyl-alcohol, wash in water and, without drying, stain for one to two minutes. Wash thoroughly in running water, dry with blotting-paper, and mount.

This method shows very well granular degenerations of the erythrocytes, the nuclei of erythroblasts and leukocytes, baso-

philic granules, and most bacteria. It is a very good stain for the malarial organism. If the film is first stained for ten to fifteen seconds in a 0.1 per cent. aqueous solution of eosin, washed, and then the methylene-blue used, a very good picture of the acid-coloring elements is given.

*Eosin and Methylene-blue.*—Fix the smear in absolute alcohol alone or mixed with an equal quantity of ether. Stain in a 0.5 per cent. solution of eosin in absolute alcohol, to which an equal quantity of water is added, for about five minutes without heating. Wash and dry, then counterstain in a saturated aqueous solution of methylene-blue for about one minute. Wash again, dry, and mount.

Gives a good picture of the nuclei of the basophilic granules and of the malarial organism: eosinophile granules stain red; the protoplasm of the polymorphonuclear leukocytes colors a slight pink; the granules remaining unstained.

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